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BIOPSY STUDIES OF CEREBRAL PATHOLOGIC CHANGES IN SCHIZOPHRENIA AND MANIC-DEPRESSIVE PSYCHOSIS

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Despite long years of study, pathologists not only are ignorant of the causation of or the factors underlying the psychoses but are even uncertain of any constant pathologic change characteristic of this state. In the present investigation an attempt has been made to attack this problem from a new angle.

It is suggested that much of the work on the psychoses has given negative results because the cerebral tissue was not obtained for examination during the life of the patient and because staining methods for oligodendroglia cells have only comparatively recently come to hand. These cells are so sensitive to change that they are rendered unfit for study during the agonal and the postmortem period that inevitably precedes necropsy.

Removal of cerebral tissue for biopsy, or *Hirnpunktion,* has been employed in Germany, especially in the differential diagnosis of dementia paralytica (Foerster[1]). However, the more recent silver impregnation methods are necessary to demonstrate clearly the so-called acute swelling of oligodendroglia cells.

The "preameboid" change in the small round glia (oligodendroglia) cells described by Rosenthal[2] was first clearly defined as acute swell-

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The words "pathologic," "physiologic" and "neurologic," etc., are used in order to conform to the terminology which is compulsory for publication in the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. We should prefer to use the words "pathological," "physiological" and "neurological."

1. Foerster, O.: Die histologische Untersuchung der Hirnrinde intra vitam durch Hirnpunktion bei diffusen Erkrankungen des Centralnervensystems, Berl. klin. Wchnschr. **49**:973-977, 1912.

2. Rosenthal, S.: Experimentelle Studien über amöboide Umwandlung der Neuroglia, in Nissl, F., and Alzheimer, A.: Histologie und Histopathologie,

(Footnote continued on next page)

ing of oligodendroglia cells by Penfield and Cone.[3] They observed severe acute swelling in a specimen taken from the region of a supposed abscess in a living patient with a cerebral embolus and mild acute swelling in a specimen obtained for biopsy from a patient in status epilepticus. This patient was not comatose or disoriented between attacks, but was drowsy. As the patient improved clinically, the authors concluded that the histologic change must also have been reversible. Most of their human material showing swelling of oligodendroglia cells was obtained at necropsy. From their experience, Penfield and Cone concluded that autolytic swelling may also develop as the result of an agonal change. It was marked when death was preceded by deep coma or stupor of several hours' duration.

Since the present investigation was commenced, important observations have been reported by Cardona,[4] who noted swelling of oligodendroglia cells in autopsy material taken from psychotic patients. There is no proof that the changes were not the result of the agonal period. In any case, the observations are of interest in view of the present discoveries.

The present investigation was undertaken at the suggestion of Dr. Wilder Penfield with a view to studying particularly the state of the oligodendroglia cells in the acute stages of psychoses and during periods of remission.[5]

CLINICAL MATERIAL

A careful selection of patients was made to avoid complicating factors, such as dehydration, fever, malnutrition, exhaustion and the use of sedatives. Consequently, in the cases summarized we chose those that represent a cross section of the schizophrenic, manic-depressive and mixed types. All the patients were at the time of operation free from any demonstrable physical illness. The conditions could not be classed as chronic, although the patients had been under observation long enough to permit a satisfactory diagnosis. We included at least 1 patient (case 19), the classification of whose disease was problematic. Only 2 patients (cases 3 and 4) were in a definitely chronic and deteriorated state. The oldest patient in the series was 40, and the youngest, 20.

Twenty-six specimens of cerebral tissue have now been obtained for biopsy from a series of 19 psychotic patients, which included 13 with schizophrenia (table 1), 5 with manic-depressive psychosis and 1 with so-called toxic encephalitis (table

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Arbeiten über die Grosshirnrinde, mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten, Jena, Gustav Fischer, 1913, vol. 6, pp. 89-160.

3. Penfield, W., and Cone, W.: Acute Swelling of Oligodendroglia: A Specific Type of Neuroglia Change, Arch. Neurol. & Psychiat. **16**:131-153 (Aug.) 1926.

4. Cardona, F.: Studio sul rigonfiamento acúto della oligodendroglia nelle psicosi, Rassegna di studi psichiat. **23**:271-281, 1934.

5. With keen interest in the investigation and helpful guidance, Dr. C. A. Porteous, Director of the Verdun Protestant Hospital for the Insane, helped in practical ways to make this work possible. His assistants, Dr. C. H. Skitch and Dr. T. E. Dancey, gave much time to each case studied.

2). A second operation was performed on 7 of the patients at the end approximately of from one to two years, and thus useful data were furnished as a control (table 3). Sixteen specimens serving as controls were taken from routine surgical material with a similar or an identical technic. Biopsies on cerebral tissue from 14 laboratory animals were made as a further check on technic, as well as in an effort to produce changes similar to those observed in clinical material.

TABLE 1.—*Tabulation of Data in Cases of Schizophrenia*

Patient	Case No.	Type of Schizophrenia	Anesthetic	Site, Occipito-parietal Region	Swelling of Oligo-dendroglia Cells
E. H.	1	Simple, rapidly deteriorating	Pentobarbital sodium; local	Left	Very marked
S. S.	2	Simple, rapidly deteriorating	Ether	Right	Marked
H. S.	3	Deteriorated	Avertin;* local	Right	None
M. T.	4	Deteriorated	Ether; morphine, ⅛ gr.; atropine, 1/100 gr.	Right	Marked
M. V.	5	Hebephrenic	Avertin; local; ether	Right	Very marked
J. H.	6	Hebephrenic	Ether	Right	Marked
P. J.	7	Hebephrenic	Avertin; local; pento-barbital sodium	Right	Very marked
F. K.	8	Hebephrenic	Avertin; local; ether	Right	Marked
P. L.	9	Hebephrenic	Ether; morphine, ¼ gr.; atropine, 1/100 gr.	Left	Slight
I. E.	10	Paranoid	Ether	Right	Marked
M. F.	11	Paranoid	Ether; morphine, ¼ gr.; atropine, 1/100 gr.	Right	Very marked
M. I.	12	Catatonic	Avertin; ether	Right	Very marked
E. S.	13	Catatonic	Ether; morphine, ⅛ gr.; atropine, 1/100 gr.	Right	None

* In this table and in tables 2 and 3, avertin with amylene hydrate was used.

TABLE 2.—*Data in Cases of Manic-Depressive Psychosis and So-Called Toxic Encephalitis*

Patient	Case No.	Type of Psychosis	Anesthetic	Site, Occipito-parietal Area	Swelling of Oligodendroglia Cells
W. L.	14	Depressed	Avertin	Right	Very Marked
R. T.	15	Depressed	Avertin; ether; atropine, 1/150 gr.	Right	Marked
V. T.	16	Manic (mixed type)	Ether; morphine, ¼ gr.; atropine, 1/150 gr.	Right	Moderate
D. R.	17	Manic	Ether	Right	Very marked
D. C.	18	Schizoid	Avertin; ether	Right	Very slight
I. W.	19	Encephalitis, type unknown	Ether; morphine, ⅛ gr.; atropine, 1/100 gr.	Right	Very marked

Sufficient material as a rule was obtained for metallic impregnation and embedding in paraffin. At operation it was possible to note any gross changes associated with the meninges and brain substance in the region under observation.

The danger of artefact in staining oligodendroglia cells is common knowledge, and in the present series an attempt was made to keep both the surgical and the histologic technic uniform, while the all-important question of rapid fixation was to a large extent solved by acquiring the material in a fresh state during operation.

SURGICAL TECHNIC [6]

A worm of brain, about 4.5 cm. in length and from 3 to 4 mm. in diameter, was obtained with the aid of a hollow cylinder, in which a gentle vacuum was established with a Luer syringe. With this, it was possible to remove the specimen

TABLE 3.—*Data in Cases in Which a Second Biopsy Specimen Was Taken*

Patient, Case No.	Type of Psychosis	Anesthesia	Site of Operation	Time Between Operations, Mo.	Swelling of Oligodendroglia Cells
E. H. 1	1. Simple schizophrenia, rapid deterioration	1. Local; pentobarbital sodium	1. Left occipitoparietal	12	1. Very marked
	2. Simple schizophrenia, rapid deterioration	2. Ether; morphine, ¼ gr.; atropine 1/150 gr.	2. Right frontal		2. Marked
H. S. 3	1. Schizophrenia with deterioration	1. Avertin; local	1. Right occipitoparietal	12	1. None (one area questionable)
	2. Schizophrenia with deterioration	2. Ether; morphine, ¼ gr.; atropine, 1/150 gr.	2. Right frontal		2. None (slight, if any)
M. T. 4	1. Schizophrenia with deterioration	1. Ether; morphine, ⅛ gr.; atropine, 1/100 gr.	1. Right occipitoparietal	14	1. Marked
	2. Schizophrenia with deterioration	2. Ether	2. Left occipitoparietal		2. Moderate
J. H. 6	1. Hebephrenic schizophrenia	1. Ether	1. Right occipitoparietal	9	1. Marked
	2. Hebephrenia in remission	2. Ether; morphine, ⅛ gr.; atropine, 1/100 gr.	2. Right occipitoparietal		2. Marked
I. E. 10	1. Paranoid schizophrenia	1. Ether	1. Right occipitoparietal	24	1. Marked
	2. Paranoid schizophrenia	2. Ether; morphine, ⅛ gr.; atropine, 1/100 gr.	2. Left occipitoparietal		2. Marked
E. S. 13	1. Catatonic schizophrenia	1. Ether; morphine, ⅛ gr.; atropine, 1/100 gr.	1. Right occipitoparietal	12	1. None
	2. Catatonic schizophrenia	2. Ether	2. Left occipitoparietal		2. Mild
V. T. 16	1. Manic-depressive, mixed type	1. Ether; morphine, ¼ gr.; atropine, 1/150 gr.	1. Right occipitoparietal	14	1. Moderate
	2. Manic-depressive, mixed type	2. Ether	2. Left occipitoparietal		2. Marked

with ease and a minimum of trauma. In patients used as controls this manipulation did not cause any noticeable reaction on the part of the sensitive oligodendroglia cells. The specimen was floated in Ringer's solution at once and in less than fifteen seconds was dropped into the fixative. The first specimen was

6. A frank discussion of the purpose and nature of the operation for removal of a biopsy specimen was always held with the patient and his relatives.

placed in a dilute solution of neutral formaldehyde U. S. P. (1:10). The second specimen was placed in a dilute solution of neutral formaldehyde U. S. P. (1: 10), Zenker's fluid or alcohol.

Procaine hydrochloride was used with 1 patient; avertin with amylene hydrate alone, with 1; avertin with amylene hydrate and a local anesthetic, with 2; avertin with amylene hydrate and ether, with 3; avertin with amylene hydrate, a local anesthetic and ether, with 2, and ether intranasally, with 10. With the 7 patients from whom a second specimen was taken, ether alone was used. Morphine and atropine were administered just before induction of anesthesia to several patients, and pentobarbital sodium, to 2. From tables 1, 2 and 3 it will be seen that the observations after any combination of these anesthetics did not indicate that swelling of oligodendroglia cells is the result of anesthesia, which is in accordance with the observations of Penfield and Cone.[3]

In most instances the initial surgical removal of a specimen for biopsy was made from the right occipitoparietal region, 6 cm. above and from 5 to 6 cm. lateral to the external occipital proturberance. In 3 patients the specimen was taken from the left occipitoparietal region. In 7 patients a second biopsy specimen was taken at the end of one or two years. In 1 patient the first specimen for biopsy was taken from the left occipitoparietal region, while the second was obtained from the right frontal region. In another patient both sets of specimens were taken from the right occipitoparietal region. In a third patient the specimen for the original biopsy was removed from the right occipitoparietal region, and the second, from the right frontal lobe. In 4 other patients the original specimen was obtained from the right occipitoparietal area, while that for the second biopsy was from the left occipitoparietal region.

HISTOLOGIC TECHNIC

For the silver staining of oligodendroglia cells, the specimen was left in a freshly changed dilute solution of neutral formaldehyde U. S. P. (1:10) for about eighteen hours. It was then frozen and cut at 16 microns, and the sections were placed in a solution of formaldehyde and ammonium bromide for from one to three hours. Impregnation was carried out in the strong silver carbonate solution of del Rio Hortega for from one to three minutes, with control by microscopic examination. Reduction was effected in a dilute solution of formaldehyde (1: 100), and the specimen was toned with a 1: 500 solution of yellow gold. A few specimens were fixed from the start in a solution of formaldehyde and ammonium bromide. No essential difference in the result was noted.

REVIEW OF THE HISTOLOGIC FEATURES OF OLIGODENDROGLIA CELLS

Preliminary to presentation of the data, it may be said that we have observed various stages of swelling of oligodendroglia cells in the cerebral hemispheres of psychotic patients. This has afforded an unusual opportunity to observe again the pathologic change itself, which was incidental to the main problem. Acute swelling of oligodendroglia cells has been described by Penfield and Cone[3] as follows:

> The mildest change is a hypertrophy marked by increase in the amount of protoplasm of the cell body and a pyknotic change of the nucleus. This is most striking in the cases in which the process is too mild to cause destruction. When

the change is taking place rapidly there is little evidence of hypertrophy. The cell body undergoes hydropic swelling and there appear unstained vacuoles outlined by granules. The expansions come to be represented by granules as the connecting protoplasm disappears. The cell body gradually disintegrates, and finally the pyknotic nucleus remains.

From the present study on psychotic patients it seems that there are two types of swelling of oligodendroglia cells. Whether one type passes into the other is uncertain, but that any stage of one type may be observed in one psychotic person indicates that as a rule each develops from the start along its own level. In the first type of swelling the nuclei are well preserved and of normal size. In the second type the nuclei are shrunken, angulated and pyknotic, and vacuolation of the cytoplasm is intensified. For purposes of discussion, the types and degrees of swelling may be classified as illustrated in figure 1. The three upper lines of cells show the development of swelling with preservation of (*n*) normal-appearing nuclei, while the lower cells demonstrate similar degrees of swelling, but with (*p*) pyknosis of the nuclei.

First degree swelling is indicated by *a*. Here, the cytoplasm is swollen; protoplasmic processes are thickened, shortened and fragmented, and early vacuolation of the cytoplasm may be seen. Second degree swelling, indicated by *b*, is characterized by marked vacuolation of the cytoplasm, and processes are hard to see. In third degree swelling, indicated by *c*, cytoplasmic distention and vacuolation are extreme. Various degrees of pyknosis of the nuclei may or may not be present in a single specimen.

From the present study of the psychoses, it appears that the change is characteristically observed in the oligodendroglia cells of the white matter alone. It may be present at all depths, to the neighborhood of the ventricle. The swelling may be patchy in distribution, in which case such areas may appear to be more cellular. If the change is not uniform throughout, one is apt to find it most readily at a depth of 1 cm. from the cortex or in the deepest layers. Furthermore, evidence will be adduced to indicate that such swelling may be long lasting—in other words, that a condition of chronic swelling of the oligodendroglia cells may exist.

HISTOLOGIC OBSERVATIONS IN SPECIMENS USED AS CONTROLS

Specimens of cerebral tissue were taken for biopsy from a series of 16 consecutive nonpsychotic patients serving as controls on whom operation was performed for a variety of causes. For many patients the operative and histologic technic was identical with that used for the psychotic patients, in that the same apparatus and methods were used by the same operator. For other patients the technic was similar,

but not necessarily identical, and in the case of 7 patients the specimen was part of a block removed at operation. Only certain points of special interest will be discussed regarding this control material, which is unlimited; otherwise, a brief summary will be presented.

Eleven of the patients were epileptic; of these, 4 were suffering from a cerebral scar, and 1, from a tumor of the brain (glioblastoma

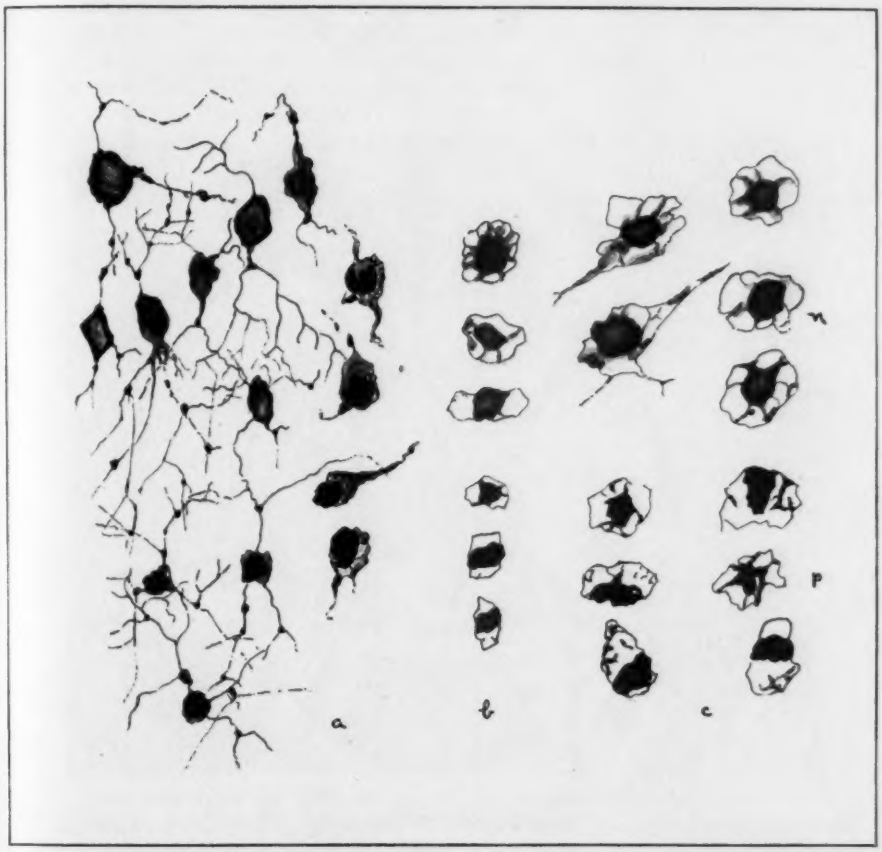

Fig. 1.—Types and degrees of swelling of oligodendroglia cells. The upper three rows (*n*) show the development of swelling with preservation of normal-appearing nuclei. The lower three rows (*p*) show similar degrees of swelling, but with pyknosis of the nuclei. First degree swelling is indicated by *a*; second degree swelling, by *b*, and third degree swelling, by *c*.

multiforme); in 6 the possibility of a tumor or the nature of the seizures was studied. Of the 5 nonepileptic patients, 1 had a tumor of the brain (astroblastoma) situated in a lobe adjacent to the site of operation; 1, an injury at birth with paralysis and athetosis; 1, an abscess of the

right frontal lobe of the brain, from the neighborhood of which the specimen was taken; 1, an adult, internal hydrocephalus, and 1, cerebral atrophy, three years after a cerebral accident.

Although it may be said that no swelling of oligodendroglia cells was seen in the majority of the 16 patients used as controls, 5 interesting and notable exceptions will be described briefly, as they appear to lend importance to, rather than to detract from, the observations made on psychotic patients.

The first patient (W. E.) was having attacks of status epilepticus associated with a cerebral scar. He was stuporous between attacks. In this instance, in

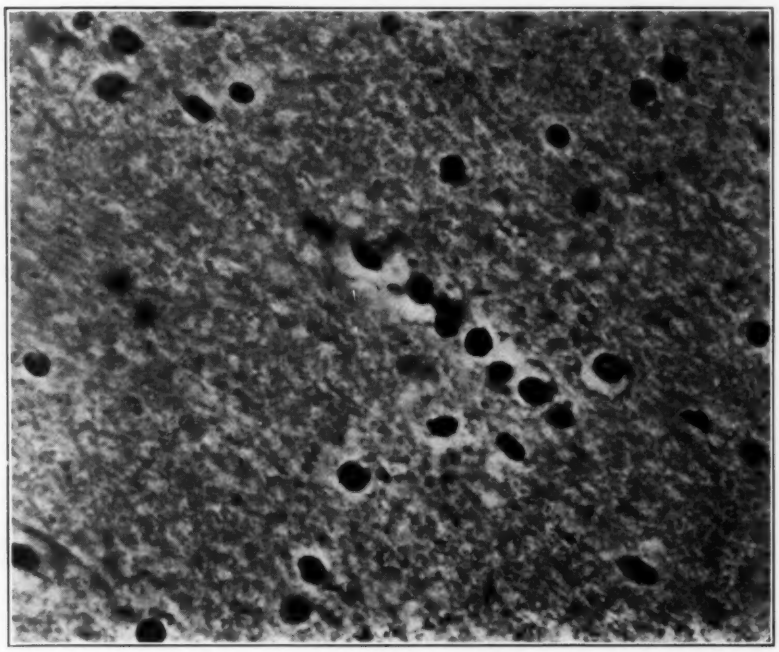

Fig 2 (W. E.).—Moderate second degree swelling of oligodendroglia cells. The specimen was obtained from a patient in status epilepticus who was stuporous between attacks.

which there was a changed mental state, moderate second degree swelling of oligodendroglia cells was discovered (fig. 2; block removed).

The second patient (P. S.) was thought to have a tumor. He was comatose and in status epilepticus, with decerebrate rigidity. Histologic examination disclosed a condition of the brain, associated with increased vascularity and perivascular infiltration with lymphocytes, plasma cells and some polymorphonuclear leukocytes, in which macrophages, fat and hypertrophied astrocytes took part, as in an acute degenerative process or hemorrhage. Poor stains showed doubtful swelling of oligodendroglia cells (block removed at operation).

A third patient (T. K.) suffered from the effects of a cerebral scar, presumably associated with "healed" localized chronic cerebritis resulting from frontal sinusitis.

The patient had an anxiety neurosis. There was an epileptic attack three hours before operation; during the latter, considerable electrical stimulation was carried out. Swelling of oligodendroglia cells was general in the block removed.

A fourth patient (S.) had a cerebral scar resulting from an injury at birth. He seemed to have a slight seizure on the operating table and during cortical stimulation frequently experienced the sensation of an impending attack. Swelling of oligodendroglia cells was present in the block removed at operation.

A fifth patient (G.) showed marked cerebral atrophy, involving chiefly the left hemisphere. There was a history of right hemiplegia, developing over a period of several days, three years before admission. The patient was admitted with the tentative diagnosis of tumor of the brain with associated headache, but there was no objective evidence of increased intracranial pressure. There was a curious shift of the ventricles from right to left, with marked atrophy of the left hemisphere. The clinical diagnosis was cerebral atrophy, with hemiplegia of unknown cause. Biopsy of cerebral tissue taken from the "normal" right hemisphere by a technic identical with that for the psychotic patients showed first, and in some instances second, degree swelling of oligodendroglia cells. The patient left the hospital before a satisfactory mental examination was made. There were no obvious unusual mental manifestations, but she was quiet and reserved. This, then, is a case serving as a control in which swelling was observed without adequate explanation. In the preceding 4 patients it was closely associated with epilepsy and, in at least 2 of these, with a changed mental state.

Of the 11 patients serving as controls in whom the oligodendroglia cells did not show swelling, the observations on only 3, which seemed to be of special interest, will be mentioned separately for comparison with those on the preceding patients.

The first patient (A. J.) had an abscess of the right frontal lobe of the brain, in the neighborhood of which one might expect to find at least some swelling of oligodendroglia cells; yet there was none (block removed; fig. 3).

The second patient (A. S.) had glioblastoma multiforme and status epilepticus with intervals of mental clarity between attacks. Here again no swelling of oligodendroglia cells was observed (block removed; fig. 4).

The third patient, a man aged 29, had marked internal hydrocephalus, of communicating type. He was mentally clear, but suffered from headache. The appearance of the optic disks was suspicious and betrayed a former period of increased intracranial pressure. The spinal fluid pressure was raised slightly above normal. From the clinical history it was concluded that the patient had passed through a period of higher pressure about two years before and, furthermore, that the cause of the condition lay in an obscure infection in early childhood. Through a subtemporal decompression, one of us freed adhesions in the region of the interpeduncular cistern. At the same time, a communication was made with a biopsy needle between the inferior horn of the lateral ventricle and the subarachnoid space. The specimen, thus removed with a technic identical with that used in taking a biopsy specimen, was saved for examination. No swelling of the oligodendroglia cells was observed.

Reports on the remaining 8 patients in whom oligodendroglia cells did not show swelling are omitted. The list could be added to indefinitely.

One may say that in patients who are mentally normal, and in the absence of an epileptic seizure, provided that there is not an inflammatory or a degenerative process in the area examined, no swelling of the oligodendroglia cells will be observed.

As a further control to the technic of obtaining specimens and their histologic preparation, biopsy was performed on a series of 12 laboratory animals. In 2 rabbits and 3 rats cerebral tissue was obtained immediately after the animals were killed, while from the remainder cerebral tissue for biopsy was removed. In all, tissues from 1 monkey, 5 cats,

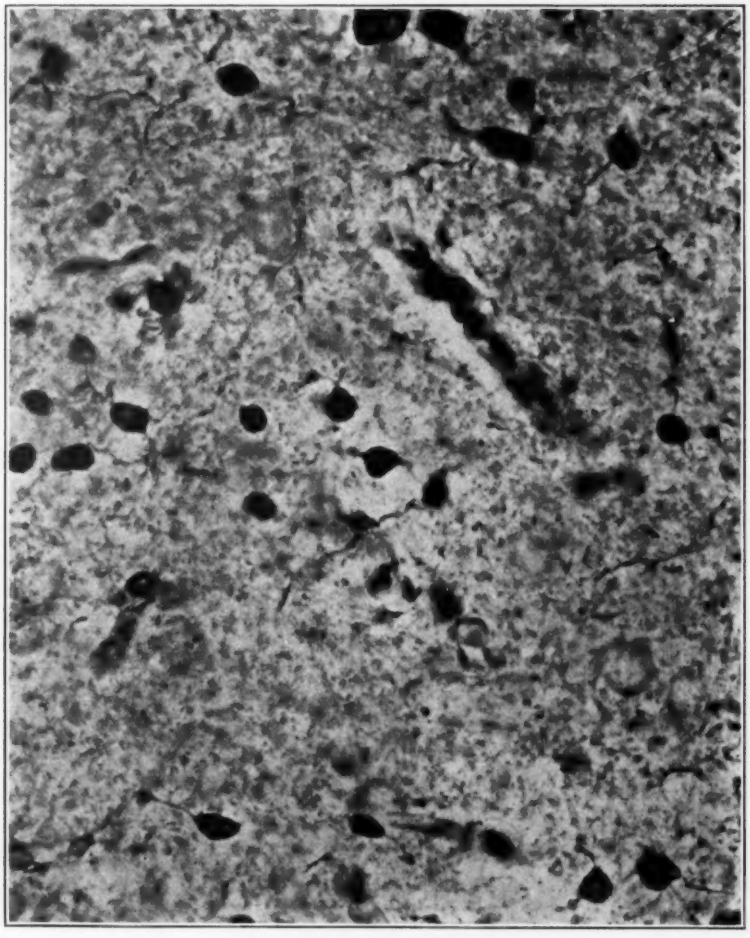

Fig. 3 (A. J.).—Normal oligodendroglia cells from the neighborhood of an abscess in the right frontal lobe of the brain.

3 rabbits and 3 rats were thus examined. In no case was there seen swelling of oligodendroglia cells. One cat and 1 rabbit had previously been given cisternal injections of spinal fluid obtained from a patient with hebephrenia and catatonia.

The technic was also controlled by removal of a second specimen for biopsy and comparison of the successive specimens. This operation

was performed on 7 of the psychotic patients, with the results noted later in the text. In 6 patients with schizophrenia, including 1 with hebephrenic, 1 with simple, rapidly deteriorating, 1 with catatonic, 2 with deteriorated and 1 with paranoid type, a second biopsy specimen was taken after intervals of nine, twelve, twelve, twelve, fourteen and

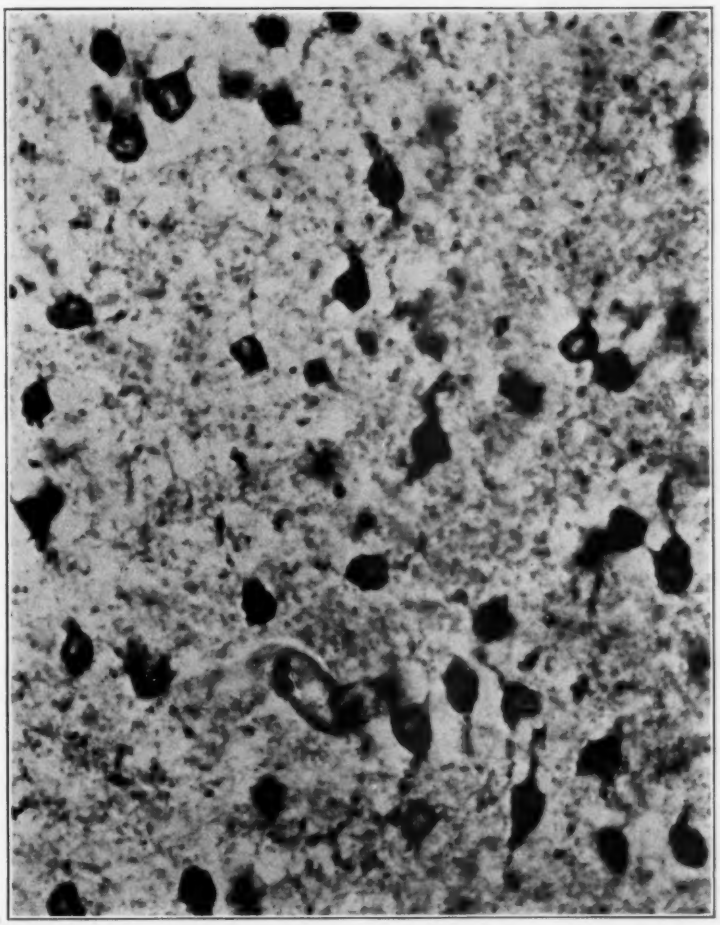

Fig. 4 (A. S.).—Normal oligodendroglia cells from the brain of a patient with glioblastoma multiforme. The patient was in status epilepticus, but was mentally clear between attacks.

twenty-four months, respectively, and in 1 patient in a manic phase of manic-depressive psychosis, after an interval of fourteen months. Similar observations at the second biopsy in all but 1 patient (and here the difference was slight) were an additional check on the technic (table 3).

Summary.—With regard to the groups of nonpsychotic patients used as controls, it may be said that swelling of oligodendroglia cells was observed in 2 patients with status epilepticus (W. E. [fig. 2] and P. S.) who were stuporous or comatose between attacks, whereas it did not occur in another patient (A. S. [fig. 4]) with repeated seizures but with a clear mental state between attacks. Swelling was observed in a third patient (T. K.) who suffered an attack three hours before exploration, at which time considerable cortical electrical stimulation was carried out, and in whom the cicatrix was associated with an old inflammatory lesion. Swelling was also observed in a fourth patient (S.) when the specimen was obtained at about the time of production of an attack on the operating table. It was discovered again in a fifth patient (G.) who had an atrophic lesion of the opposite cerebral hemisphere, which was not diagnosed, but had given rise to symptoms of tumor of the brain without special mental change. The patient, however, was not investigated from the psychiatric point of view.

In all other clinical and experimental specimens there was absence of swelling of oligodendroglia cells. One may repeat that swelling of oligodendroglia cells does not occur in mentally normal persons, provided there has been no recent epileptic seizure or there is no inflammatory or degenerative process in the area examined. This observation is in contrast to that for psychotic patients (tables 1, 2 and 3 and the following case histories). In all but 3 of the 19 psychotic patients, a considerable degree of swelling of the oligodendroglia cells was observed.

BIOPSIES ON CEREBRAL TISSUE FROM PATIENTS WITH SCHIZOPHRENIA [7]

CASE 1.—*Simple, rapidly deteriorating type.*

History.—E. H., a woman aged 28, was admitted on April 18, 1932, with an illness of indefinite onset. She had been married at the age of 23 and was frigid. A child was born three years after the marriage and lived one day; the patient came to the hospital four months later because for several weeks she had been depressed, worried, uninterested in her surroundings and impulsive and had threatened suicide.

Positive Physical Findings Since Admission.—The blood pressure was 140 systolic and 68 diastolic. The skin was thick, pale and oily, with acne over the face. The lower extremities were hirsute. There was possibly early left homonymous hemianopia in the upper quadrants. The tendon reflexes were hyperactive. The right plantar reflex was normal; the left was of indeterminate extensor type.

Course.—Throughout the illness the patient was anxious to cooperate to the extent that she talked coherently about the peculiar lack of emotion that had begun

7. The ages given are approximately those at the time of taking the first biopsy specimen.

when "something snapped in the back of her head" and resulted in a feeling of tension. This tension was sometimes described as ambivalent thinking; it at times produced ritualistic, and at others impulsive and negativistic, behavior. A year before the first operation, two years after admission, deterioration set in gradually and was well established by the date of the second operation. The operations did not appear to affect the course of the disease in any way, and deterioration has been and is progressive.

Laboratory Findings.—The Wassermann reaction of the blood was negative; there was an occasional trace of albumin in the urine.

First Operation.—The first specimen for biopsy was taken on March 7, 1934, in the left occipitoparietal region, to a depth of 4 cm. This was followed by ventriculographic examination. Local anesthesia was induced with procaine hydrochloride without epinephrine, supported by 4½ grains (0.29 Gm.) of pentobarbital sodium. The scalp was very vascular; the dura mater was unusually tender and overrun by many fine blood vessels. The brain was under moderate pressure. The cortex was grayish yellow, and the neighboring sulcus was deep. The consistency was rather firm. Ventricular puncture did not show increase in pressure, and 35 cc. of oxygen was injected. A bubble of air was found at each frontal pole. The rest collected over the frontal lobes.

Histologic Observations: The general architectonic was normal. There were areas in which clusters of nerve cells were elongated and fusiform, with shrunken, pyknotic nuclei, centrally placed, and glazed cytoplasm, which had deeper staining qualities than usual. These cells lay close to the white matter. Their appearance may be considered to be an artefact; in any case they were seen in surgical specimens taken as a routine. The astrocytes were normally spaced, and their processes were inclined to be long. Occasional swollen cells were present, but on the whole the structure was probably normal.

The oligodendroglia cells, on the other hand, showed marked generalized swelling (*a, b* and *c* types, figs. 1 and 5 *A*) throughout the white matter, being maximal at depths of 0.5, 1 and 3 cm. below the cortex, and pyknosis of the nuclei was marked (fig. 5 *B*). The microglia cells were normal in appearance, and the vessels were not unusual. The mucicarmine stain showed nothing unusual.

Second Operation.—The second biopsy specimen was taken on March 11, 1935, twelve months after the first. The patient was more deteriorated, but less agitated. The specimen was taken from the right frontal region, from a depth of 3.5 cm. Ether was used intranasally, supported by ¼ grain (0.016 Gm.) of morphine sulfate and 1/150 grain (0.4 mg.) of atropine sulfate. Large diploic vessels were seen. The middle and inner portions of bone and the dura were reddish. A large amount of clear fluid, which was probably of subarachnoid origin, escaped when the dura was opened.

Histologic Observations: The nerve cells were not unusual. The astrocytes were large, but normal. There was, however, marked generalized swelling of the oligodendroglia cells (*a* and *b* types) throughout the white matter (fig. 6).

CASE 2.—*Simple, rapidly deteriorating type.*

History.—S. S., a woman aged 24, had become depressed, agitated and suicidal a few months previous to admission. She said that she had noted the onset six years previously in sudden inability to control her thoughts.

Positive Physical Findings Since Admission (March 31, 1934).—There was a systolic murmur; the blood pressure was 110 systolic and 70 diastolic, and exercise reserve was good. Other findings were: chronic tonsillitis; prolapse

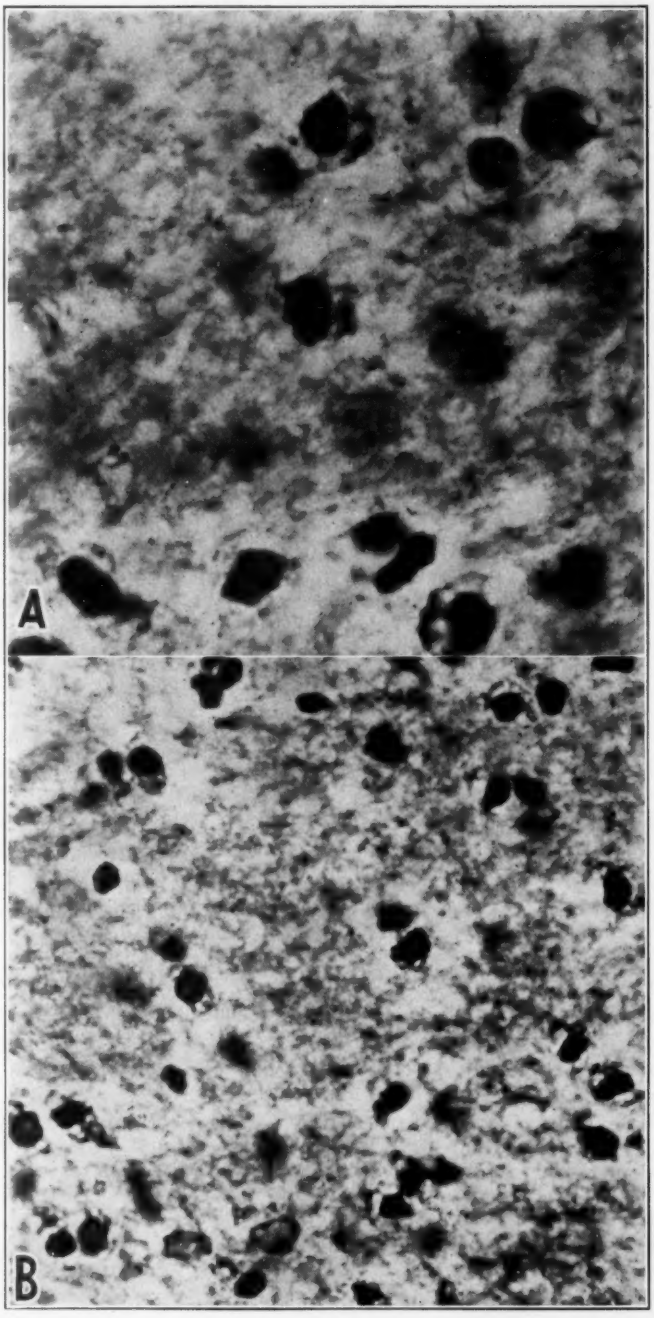

Fig. 5 (case 1).—Specimen taken for biopsy from the left occipitoparietal region of a patient with simple schizophrenia (rapidly deteriorating). *A*, marked generalized third degree swelling of the oligodendroglia cells is shown. *B*, pyknosis of the nuclei is evident.

of the right ovary; slight erosion of the cervix; male distribution of hair, and thick, pale, oily skin, with acne.

Course.—For several months after admission the patient considered herself an invalid and complained of many symptoms, some of which were based on the fact that she had been treated as an invalid without due cause all her life. It became apparent that the complaints were attempts to rationalize a feeling of tension, which was consistently present. The patient complained that she was unable to experience any emotion, that her mind was clear, but always driving her, and that it felt as though at times it were working in two directions (ambivalence). Deterioration was beginning at the time of the first operation and is progressing.

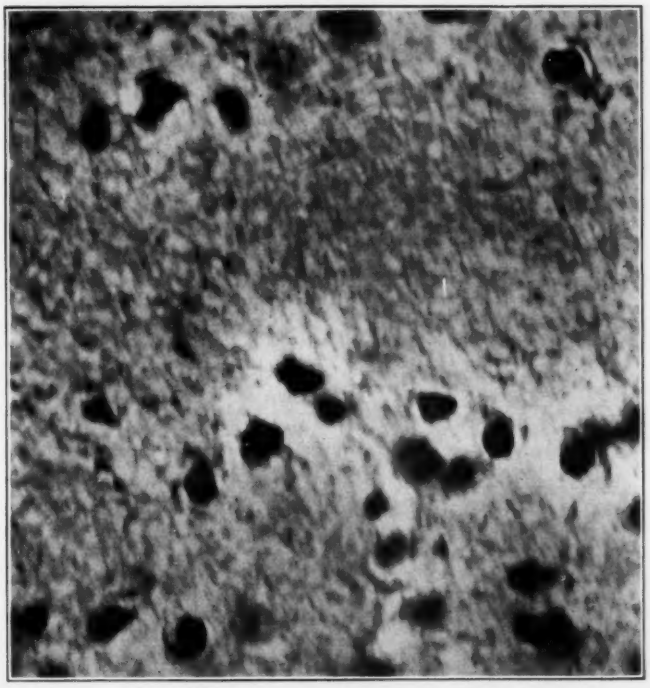

Fig. 6 (case 1).—Photograph of second specimen taken for biopsy one year later from the right frontal region. This specimen shows at least second degree swelling of oligodendroglia cells.

Laboratory Findings.—The Wassermann reaction of the blood was negative; the protein and sugar contents and the cell count of the blood and the results of urinalysis were normal.

Operation.—On Feb. 18, 1935, cerebral tissue was taken for biopsy in the right occipitoparietal region, to a depth of from 3.5 to 4 cm. Anesthesia was induced by intranasal administration of ether. There was no abnormal collection of subdural fluid. The subarachnoid space was shallow. The surface of the brain was a normal gray-yellow color. The adjacent sulcus was shallow.

Histologic Observations: The nerve cells appeared normal; the few which were pyknotic were probably artefacts. The astrocytes were normal. There was

marked swelling of oligodendroglia cells (*a* and *b* types), which in some areas became more intense (*a*, *b* and *c* types, fig. 1).

CASE 3.—*Deteriorated type.*

History.—H. S., a man aged 26, had an illness the onset of which was gradual. It probably began in adolescence, as the patient was unable to complete school. More acute symptoms appeared four years before admission.

Positive Physical Findings Since Admission (Dec. 16, 1933).—Appendectomy had been performed before admission. There was bradycardia, the pulse rate being 50. The patient had weakness of the left side of the face, of the upper motor neuron type. The tendon reflexes were depressed; plantar flexion was present, with fanning of the toes.

Course.—On admission, over a year before operation, the patient presented a picture of deteriorated schizophrenia. He was untidy, preferred to stare at himself in the mirror and seldom replied to questions; the replies which were obtained were incoherent or disconnected. Such was his condition at the time of the first and second biopsies.

Laboratory Findings.—Urinalysis showed a trace of albumin. The Wassermann reaction of the blood was negative. The urea nitrogen of the blood was 11 mg.; phosphorus, 4 mg., and calcium, 9.8 mg., per hundred cubic centimeters. The level of sugar in the blood was normal, being 103 mg. per hundred cubic centimeters.

First Operation.—On March 14, 1934, cerebral tissue was taken for biopsy from the right occipitoparietal region, to a depth of 4 cm. The anesthetic used was avertin, with procaine hydrochloride locally. When the dura was opened, there was observed an abnormal collection of subdural fluid, which was only fairly well demonstrated to be subdural. However, displacement of the brain allowed considerable fluid (subdural?) to escape, while puncture of the pia, which must simultaneously have ruptured the arachnoid, caused a steady flow of what seemed to be subarachnoid fluid. The arachnoid was, for some reason, difficult to recognize in this case. The cortex was grayish and translucent, with evidence of atrophy. The cerebral pressure was normal. (Seven days after the operation the patient answered and laughed, which he did not do before; in other words, he was somewhat brighter.)

Histologic Observations: The nerve cells were normal, with interspersed cells showing pyknosis, probably an artefact. There was an area of moderate astrocytic reaction. These cells had thickened, shortened and rather abundant processes, and one section showed increase in the size of the cell body. The oligodendroglia cells were somewhat sparsely scattered, but were normal in appearance and showed no swelling. Figure 7 represents the only area the normality of which might be questioned.

Second Operation.—A second biopsy specimen was taken on March 18, 1935, in the right frontal region. Since the former procedure, there had been some gain in weight. Ether was given intranasally, with ¼ grain (0.016 Gm.) of morphine sulfate and 1/150 grain (0.4 mg.) of atropine sulfate. The bone was thick, and the inner table, hard. The subarachnoid space was fairly deep, but the arachnoid was thick, spongy, and somewhat opaque. The cortex was of normal color, though it was not well seen through the haze of arachnoid.

Histologic Observations: The nerve cells and the astrocytes were normal. The oligodendroglia on the whole seemed to show slight, if any swelling (fig. 8).

CASE 4.—*Deteriorated type.*

History.—M. T., a woman aged 25, six months before admission became excitable and impulsive, but quieted for a time, when it was noted that she was

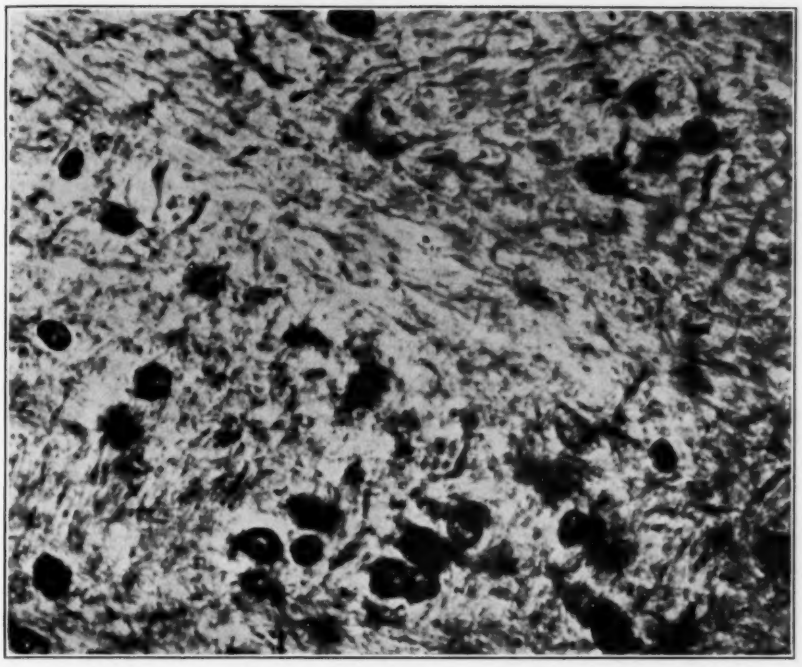

Fig. 7 (case 3).—Specimen taken for biopsy from the right occipitoparietal region in a case of schizophrenia, of deteriorated type. Oligodendroglia cells are sparsely scattered. This area was the only one in which the appearance was questionable; otherwise, the cells were normal.

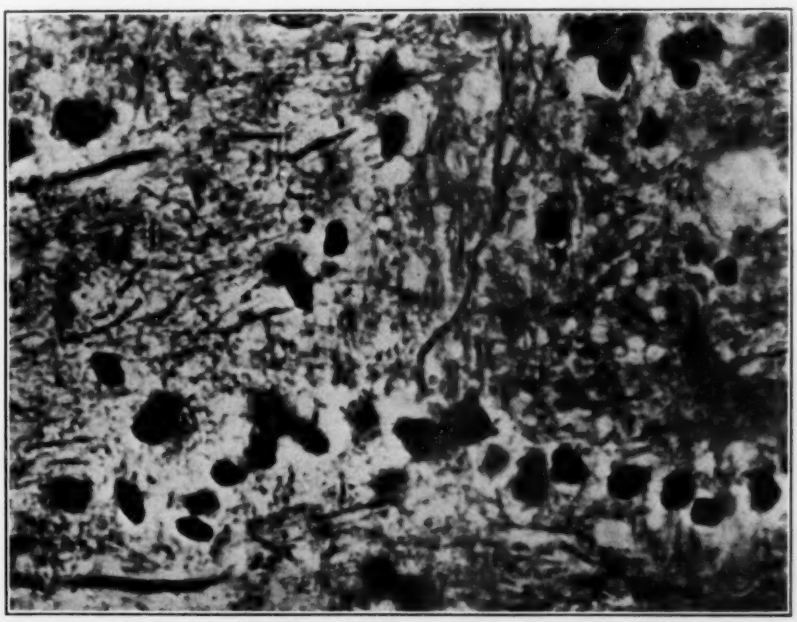

Fig. 8 (case 3).—Section of a second specimen taken for biopsy from the right frontal region in the same case as that in figure 7. The oligodendroglia cells showed slight, if any, swelling, which was most evident in this area.

uninterested, neglectful and preoccupied. Two weeks before admission she became violent and destructive. She had two illegitimate children.

Positive Physical Findings Since Admission (March 10, 1932).—The patient was of asthenic physique and poorly nourished. On admission the physical condition was good; she had had no illness since admission. Physical examination before the biopsy specimen was taken failed to demonstrate any clinical signs of organic disease.

Course.—On admission the patient was indifferent, preferred to sit by herself and was preoccupied, occasionally smiling for no aparent reason. She conversed readily with some members of the staff and was negativistic with others. Her conduct was good except that she was untidy and occasionally had an impulsive episode, when she attacked some one near her or destroyed furniture. This appeared to be a reaction to auditory hallucinations; these could not be demonstrated, however, nor would the patient explain her reason for such behavior. These impulsive episodes became more frequent; she became more apathetic and less communicative; her general appearance also changed gradually. Without symptoms of organic disease, she appeared to age and, altogether, presented the picture of so-called deterioration at the time of operation, in which condition she remains at present.

Laboratory Findings.—Urinalysis showed a trace of albumin.

First Operation.—Cerebral tissue was taken for biopsy on April 15, 1935, in the right occipitoparietal region. As anesthetic ether was used intranasally, with ⅛ grain (0.008 Gm.) of morphine sulfate and 1/100 grain (0.6 mg.) of atropine sulfate.

Histologic Observation: The nerve cells and astrocytes were not unusual. The oligodendroglia cells semed less numerous than normal, with a fairly marked degree of swelling (*a* and *b* types) and pyknosis of the nuclei.

Second Operation.—A second biopsy specimen was taken in the left occipitoparietal region on June 10, 1936, to a depth of 4.5 cm. Ether was given intranasally. The presence of subdural fluid was not proved, but much fluid (subdural?) was obtained when the brain was displaced from the burr opening. The subarachnoid space locally appeared normal. The brain was under moderate pressure. The cortex was dusky gray-yellow. There was a slight general increase in resistance to passage of the needle and the specimen was inclined to be brittle.

Histologic Observation: The nerve cells were not unusual, but the astrocytes had thick, short processes. The oligodendroglia cells showed signs of moderate swelling, which appeared indefinite, owing to poor impregnation.

CASE 5.—*Hebephrenic type.*

History.—M. V., a woman aged 20, became ill suddenly. She had refused food one month before admission. She tried to go out alone at inconvenient times and was violent when opposed, suicidal and destructive. She complained that her fiancé had used a needle on her about six months before admission.

Positive Physicial Findings Since Admission (Oct. 3, 1933).—The patient was of asthenic, juvenile type, and this habitus was seen in all the siblings. The blood pressure was 105 systolic and 75 diastolic. The tendon reflexes were hyperactive. The uterus was infantile, and the patient had had periods of amenorrhea. There was a birth mark over the back of the neck, and a groove extending up to the external occipital protuberance was palpable in the midline. There was a history of frontal headaches when the patient was at school.

Course.—On admission the patient was agitated, resistive, noisy and uncleanly. She later became mute and negativistic. She soon adjusted herself to hospital

routine, but remained uninterested, impulsive and given to fantasy and ambivalent thinking. Removal of a specimen from the right parieto-occcipital region for biopsy was uneventful until the eleventh day after the operation when the patient had a jacksonian seizure. The attack appeared to begin with emesis, followed by twitching in the right hand. This was followed by turning of the eyes and head to the left and fluttering of the eyelids; a general convulsion then lasted a few minutes and was followed by confusion and amnesia for the attack. Physical examination was made one hour and a half after the attack, with the following significant findings: tendon reflexes, three plus; a Hoffmann sign, palmomental reflex and transient planter extension on the right side, and abdominal reflexes in all four quadrants.

An encephalogram was made on March 3, 1935, 70 cc. of fluid being replaced by air. There were no unusual findings; the ventricles were partially filled, symmetric and not enlarged. A low grade fever developed after the encephalogram. No cause for this could be found for a month. Then the patient became jaundiced and recovered within a few days. There have been no other seizures. The patient's physical condition has remained good; she has not improved mentally, but prefers to remain by herself, smiling in a silly manner or doing peculiar, mischievous tricks.

Laboratory Findings.—The Wassermann reactions of the blood and spinal fluid were negative. Urinalysis gave normal results except that bile pigment was discovered during the period of jaundice. Culture of material from the throat was sterile, and examination of the stools gave nothing abnormal.

Operation.—On May 10, 1934, cerebral tissue was taken for biopsy in the right parieto-occipital region, to a depth of 4.75 cm. Avertin anesthetic, local and ether were used. No abnormal collection of subdural fluid was observed, and little subarachnoid fluid escaped. The brain was under moderate tension. Ether given half-way through the operation caused the brain to bulge markedly into the bur hole. The cortex was grayish yellow. Sulci were not seen, but probably were not deep. The brain tissue seemed of normal consistency.

Histologic Observation: Many pyknotic nerve cells were present. The astrocytes were considerably changed. They were small, widely spaced and sparse. The cell bodies were deeply stained and irregular and their processes as a rule were short, thickened and unusually wavy. The oligodendroglia cells showed swelling, which was mild just beneath the gray matter, more marked at a depth of from 1 to 2 cm. and most marked (*a*, *b* and *c* types) at the deepest levels. Many had angulated pyknotic nuclei (fig. 9). Swollen cells occurred in the same area with others which were only slightly swollen or cells which showed no cytoplasmic change but had angulated, pyknotic or small nuclei.

Case 6.—*Hebephrenic type.*

History.—J. H., a woman aged 21, became ill suddenly a year prior to admission. She had trancelike episodes, was argumentative, showed quarrelsome behavior and ran away from home unclad. She was emotionally unstable and suicidal and threatened to kill her mother.

Positive Physical Findings Since Admission (April 25, 1932).—The patient was of masculine type. She had trichosis over the upper lip, an infantile uterus, with periods of amenorrhea, and a basal metabolic rate of minus 14 per cent. The lower abdominal reflexes on the right were less active than the upper. There was physical and mental improvement after the administration of pituitary extract prepared by the method of Collip, in April 1934, and desiccated thyroid, in February

1936. The patient was under observation during this period, and a low grade fever of unknown origin was noted. This disappeared when the physical and mental condition improved.

Course.—The patient gave a history of dissatisfaction with the home conditions, resentment against her mother's talkativeness and a conflict concerning masturbation. During the course of the illness she was fairly well adjusted with regard to conduct for periods of from two to three weeks. At the time of writing, she expresses ideas of strangeness, and her emotions are not adequate to the situation. These comparatively good periods are suddenly interrupted by confused, noisy, self-mutilating and destructive episodes. The patient is not amnesic for these periods, and it has frequently been noted that they almost invariably follow any discussion concerning her mother or the possibility of going home. This was the condition at the time of the first operation. The patient improved sufficiently

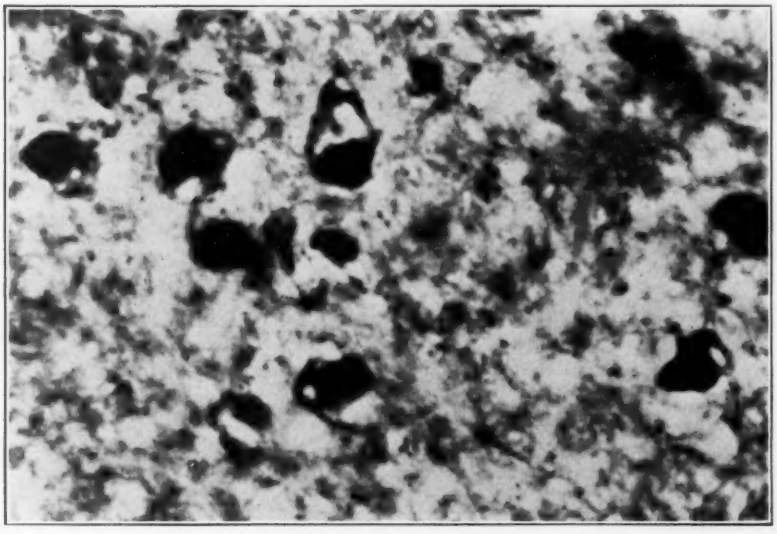

Fig. 9 (case 5).—Specimen taken for biopsy from the right occipitoparietal region in a case of hebephrenia. Swollen oligodendroglia cells may be seen with angulated, pyknotic nuclei. Compare with figure 1.

to go home in February 1935. She was fairly well adjusted, and while comparatively well, she returned to the hospital for the second operation. She was readmitted one month after this operation; the episodic attacks have continued until the present.

Laboratory Findings.—The Wassermann reaction of the blood was negative, and urinalysis gave normal results.

First Operation.—On June 27, 1934, cerebral tissue was taken for biopsy in the right occipitoparietal region, to a depth of 4.5 cm. As anesthetic ether was given intranasally. The bone was unusually thick and vascular. There was no subdural fluid. The brain was under moderately increased pressure, undoubtedly the result of the anesthetic. The cerebral cortex was yellowish brown. The presenting convolution was round and narrow, and the neighboring sulcus, probably deep. On puncture, there was some superficial resistance, which may have been

due to the pia mater. The brain felt more resistant as the deeper layers were pierced, especially on the first puncture. The general appearance of the cortex was that of fairly marked atrophy, although in normal brains one perhaps sees smaller convolutions in the occipitoparietal region than elsewhere. The increased resistance to advance of the hollow needle tended to confirm the presence of atrophy.

Histologic Observations: Some pyknotic nerve cells were present. The astrocytes had undergone chronic hypertrophy. The oligodendroglia cells showed a marked degree of swelling (*a* and *b* types; fig. 10).

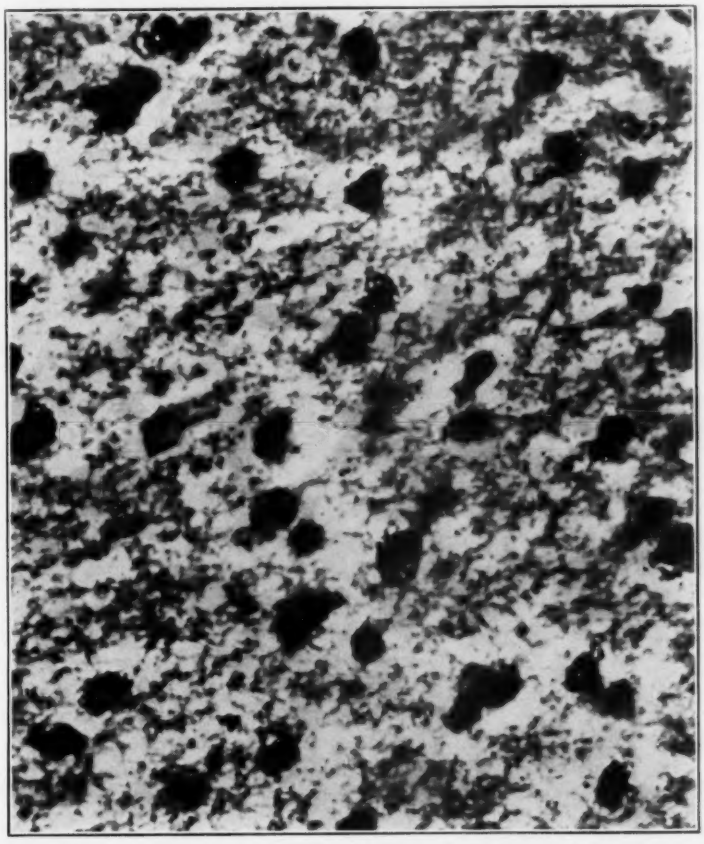

Fig. 10. (case 6).—Specimen taken for biopsy from the right occipitoparietal region in a case of hebephrenia, showing oligodendroglia cells with marked swelling.

Second Operation.—A second specimen was taken for biopsy on April 8, 1935, in the right occipitoparietal region to a depth of 3.5 cm. The anesthetic used was ether, preceded by ⅛ grain (0.01 Gm.) of morphine sulfate and 1/100 grain (0.6 mg.) of atropine sulfate. The former scar extended to the dura only. There were no arachnoid adhesions to the dura and no evidence of cerebral scar. The subarachnoid space was seen to be deep when the brain was displaced. The brain

was under moderate tension. The cortical surface as seen through the dura was yellowish brown. The brain seemed to offer a little more resistance than usual in the outer layers, which became fairly marked in the deepest strata. This was observed with taking of both specimens. On withdrawal of the specimen the brain tissue was seen to be slightly elastic.

Histologic Observations: The nerve cells and the astrocytes were not unusual. The oligodendroglia cells were again markedly swollen (*a* and *b* types).

CASE 7.—*Hebephrenic type.*

History.—P. J., a woman aged 28, five months before admission became excited, shouting, singing and crying; was distractible and impulsive, and suffered from auditory hallucinations. She recovered from two such attacks, which lasted but a short time, before being admitted to the hospital, in much the condition described.

Positive Physical Findings Since Admission (March 6, 1932).—The patient was of juvenile, dysplastic type. The tendon reflexes were somewhat exaggerated on admission.

Course.—After admission the patient's conduct improved gradually. She was allowed to go home on trial on Oct. 16, 1932. She became disturbed at home and was readmitted on March 10, 1933, after a suicidal attempt, when she sustained a fracture of the right elbow. This fracture was reduced by open operation. While in the hospital, the patient was overactive, troublesome, negativistic and interfering, and such was the condition at the time of taking the first biopsy specimen. She improved somewhat after this operation and was allowed to go home on trial on June 2, but returned at the end of a week, noisy and disturbed. She improved during the course of several weeks, but was somewhat euphoric, impulsive and agitated at times. She was allowed to go home on trial on Nov. 6, 1935, and remained away from the hospital until April 1937.

Laboratory Findings.—Urinalysis revealed an occasional trace of albumin and once a trace of sugar. The Wassermann reaction of the blood was negative.

Operation.—On April 25, 1934, cerebral tissue was taken for biopsy in the right occipitoparietal region, to a depth of 4.5 cm. The anesthetic used was avertin and 3 grains (0.195 Gm.) of pentobarbital sodium. The brain was under moderate, but normal, pressure. No subdural fluid was seen. The arachnoid appeared normal. The cortex was yellowish, but could not be considered definitely abnormal. A shallow sulcus was present. The texture of the brain seemed normal as the needle was inserted, some resistance being felt at a depth of 4 cm.

Histologic Observations: Some ganglion cells near the periphery of the section showed apparent pyknosis, which was probably an artefact. The astrocytes were small and deformed and possessed numerous curly processes, which may have been slightly hypertrophied. The oligodendroglia cells showed marked uniform swelling (*c* type), most marked at a depth of 3.5 cm. (fig. 11).

CASE 8.—*Hebephrenic type.*

History.—F. K., a woman aged 24, three months before admission, when she was in the eighth month of pregnancy, had a terrifying nightmare, during which she thought that evil spirits were going to take her away. After this, she kept the household awake each night, crying and laughing at intervals because of auditory, visual, olfactory and cutaneous hallucinations. She attempted suicide by strangulation. After the birth of the baby, she thought that she was dying and frequently called the doctor because she believed that she had been infected by the nurse.

Positive Physical Findings Since Admission (Dec. 18, 1932).—The patient was in good physical condition and well nourished; she was not dysplastic. A foreign body (gauze) was removed from the vagina.

Course.—Although the patient had experienced almost continuous auditory and visual hallucinations, she was a good worker in the ward; she was pleasant and cooperative, but lacking in initiative; if left by herself she was inactive and tended to remain alone. On admission her conversation was disconnected and bizarre. Such was the condition at the time of taking the first biopsy specimen. One hour after the operation the patient became acutely ill; respirations were extremely rapid; she was pulseless, cyanotic and unconscious. A diagnosis of collapse of the left lung was made; the patient responded well to treatment and was out of danger after two hours. The mental condition did not improve, and she is now becoming somewhat untidy in habits.

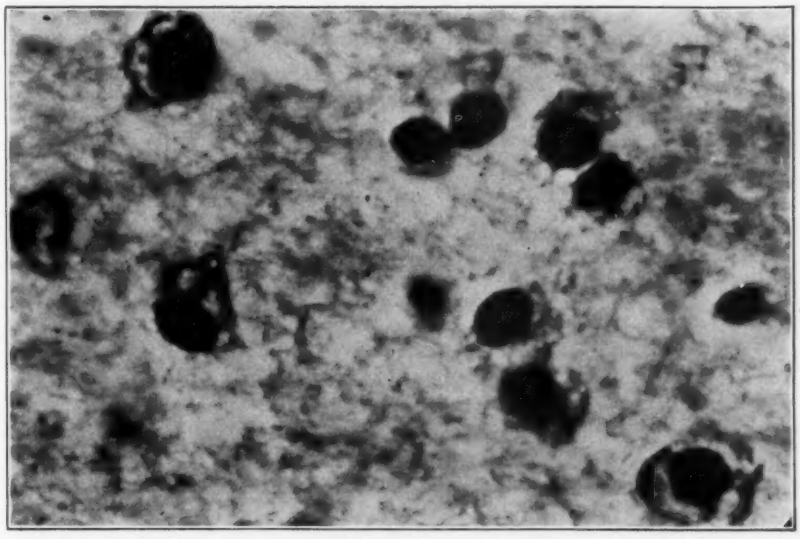

Fig. 11 (case 7).—Specimen taken for biopsy from the right occipitoparietal region in a case of hebephrenia. Oligodendroglia cells exhibit marked swelling. Compare with figure 1.

Laboratory Findings.—Urinalysis showed an occasional trace of albumin. The Wassermann reactions of the blood and spinal fluid were negative.

First Operation.—On May 2, 1934, a specimen of cerebral tissue was taken for biopsy in the right occipitoparietal region, to a depth of 4.5 cm. Anesthesia was induced with avertin, procaine and intranasal administration of ether. There was no increase in pressure and no abnormal collection of subdural fluid. The subarachnoid space was shallow. Ether had to be given for restlessness, and the cerebral pressure was then raised. The cortex was gray yellow and somewhat translucent. On the first puncture of the needle, the brain felt slightly more resistant than normal.

Histologic Observation: The nerve cells were not unusual. The astrocytes had long, curly processes. There were patches of apparent gliosis, especially in the inner and middle thirds of the specimen. The oligodendroglia cells showed marked

uniform swelling (*a* and *b* types), mostly in the central 2 cm., less marked in the superficial layer and disappearing in the deepest centimeter. In some patches of apparent gliosis swelling of oligodendroglia cells was maximal; in others it was not a feature. Most of the nuclei were large.

CASE 9.—*Hebephrenic type.*

History.—P. L., a man aged 25, six months before admission became secretive and uncommunicative and threatened injury to his parents and himself. The patient's father at that time was in a hospital for mental diseases and has since died there.

Positive Physical Findings Since Admission (Nov. 8, 1933).—The patient was in excellent condition on admission and remained so, except for an attack of cholecystitis in 1934 and German measles on April 1, 1936.

Course.—The patient was an excellent worker on the farm after his admission. He consistently denied having disorders in conduct and had no insight into his condition. He offered no spontaneous conversation with any one, but replied to questions quickly and briefly; in a similar manner he obeyed commands in a quick, automatic manner. He could not, however, describe or account for his apparent lack of interest in life; judging from his conduct, one would conclude that he was entirely preoccupied with his own thoughts and uninterested in his future. He showed no emotional reactions, but occasionally smiled for no apparent reason. Such was the condition at the time of operation.

Laboratory Findings.—Urinalysis showed an occasional trace of sugar. The Wassermann reactions of the blood and cerebrospinal fluid were negative, and the urea and sugar contents of the blood were within normal limits.

Operation.—On April 23, 1936, cerebral tissue was taken for biopsy in the left occipitoparietal region, to a depth of 4.5 cm. Ether was used intranasally, with ¼ grain (0.016 Gm.) of morphine sulfate and 1/100 grain (0.6 mg.) of atropine sulfate. There was a subdural collection of fluid. The subarachnoid space locally appeared normal. The brain was under increased tension, undoubtedly the result of the anesthetic. The cortex was dusky yellow gray. In taking the second specimen, rather firm resistance was met at a depth of 4 cm., which may have been the wall of the ventricle. The brain tissue was slightly elastic.

Histologic Observations: Some of the nerve cells appeared pyknotic and elongated. The astrocytes were rather large. There was a slight amount of swelling of oligodendroglia cells, especially in the central strata of the biopsy specimen, with some pyknosis of the oligodendroglia nuclei.

CASE 10.—*Paranoid type.*

History.—I. E., a woman aged 34, became ill two years before admission; there was a history of a short nervous attack twelve years before admission. Previous to the present admission, the patient threatened suicide and had auditory hallucinations.

Positive Physical Findings Since Admission (June 14, 1933).—The patient was of thin, asthenic type. She suffered from chronic tonsillitis, for which she underwent operation on Oct. 30, 1933.

Course.—The patient experienced visual hallucinations at night and also had auditory hallucinations, which were sometimes pleasant and sometimes disturbing. This resulted in delusions of reference and auditory and visual illusions. The patient attempted to organize her ideas into a paranoid system of persecution, but continued to adjust herself well in the ward, considering her psychosensory disturbances. Such was the condition at the time of operation.

Laboratory Findings.—The Wassermann reactions of the spinal fluid and blood were negative, and urinalysis revealed nothing abnormal.

First Operation.—On June 20, 1934, cerebral tissue was taken for biopsy in the right occipitoparietal region, at a depth of 4.5 cm. Ether was given intranasally. The brain was under normal pressure. There was no subdural fluid. The arachnoid was of normal transparency and glistening, but on puncture there was no escape of fluid in the region of a sulcus over which the arachnoid was thick and jelly-like, though still transparent. However, when the brain was displaced, considerable cerebrospinal fluid escaped. The cortex was more yellowish than normal. The consistency of the brain on first puncture was firmer than normal, and the resistance increased as the deeper layers were pierced. The yellow color of the cortex, the large subarachnoid space and the slightly increased resistance of the brain tissue bespeak mild cerebral atrophy or gliosis.

Histologic Observations: The nerve cells were not unusual. There were moderate hypertrophy of the astrocytes and marked generalized swelling (*a* and *b* types) of the oligodendroglia cells.

Second Operation.—A second specimen of cerebral tissue was taken for biopsy on June 17, 1936, in the left occipitoparietal region, at a depth of 4.5 cm. The patient was under anesthesia induced with intranasal administration of ether, supported by ⅙ grain (0.011 Gm.) of morphine sulfate and $\frac{1}{100}$ grain (0.6 mg.) of atropine sulfate. There was some fluid in the subdural space. The arachnoid was difficult to separate from the pia, though normal in appearance and translucent. The cortex was slightly yellowish gray—too much to be normal. The convolutions appeared narrow. The brain was under moderate tension. The pressure increased just before the specimens were taken, probably as a result of the manipulations. The consistency of the brain was nearly normal. The specimen seemed to come away so easily in one piece as possibly to denote the presence of some changes.

Histologic Observations: The astrocytes showed long, curly, rather stout processes. The oligodendroglia cells were markedly swollen (*a* and *b* types), especially in the deeper layers.

CASE 11.—*Paranoid type.*

History.—M. F., a woman aged 31, became ill gradually and was admitted because, in addition to peculiar and suspicious behavior, which had been present for some time, she began to express ideas of persecution, including the idea that her food was poisoned and that she had been operated on and a tube passed into her navel to make her more sociable.

Positive Physical Findings Since Admission (Oct. 4, 1932).—The patient was of thin, asthenic type, with atrophy of the retina. The blood pressure was 105 systolic and 70 diastolic. The uterus was infantile.

Course.—After admission, until the present, the patient has been cooperative with regard to examinations, nursing care and routine in the ward. She prefers to remain by herself and considers herself superior to other patients, misunderstood by the world and not called on to receive any attention from the medical staff. During examination she expressed delusions of persecution that were fairly well organized but usually did not result in severe disorders of conduct. She is given to fantasies, and auditory hallucinations appear to be present. There was a history of a difficult economic struggle. The condition has remained practically unchanged up to the time of the operation and since.

Laboratory Findings.—The Wassermann reaction of the blood was negative, and urinalysis revealed nothing abnormal.

Operation.—On April 24, 1935, cerebral tissue was taken for biopsy in the right occipitoparietal region, at a depth of 4.5 cm. Ether was used intranasally,

preceded by 1/8 grain (0.011 Gm.) of morphine sulfate and 1/100 grain (0.6 mg.) of atropine sulfate. There was no collection of subdural fluid. The subarachnoid space was shallow. The cortex was light, yellow gray and translucent. The brain showed a slight increase in resistance to the advancing needle.

Histologic Observations: The nerve cells and astrocytes were not unusual. There was marked general swelling (*a*, *b* and *c* types) of oligodendroglia cells, involving particularly the deep layers of the white matter (fig. 12). None was present in the gray matter.

Case 12.—*Catatonic type.*

History.—M. I., a woman aged 28, six years before admission was somewhat excited and disturbed for several months; she was then quieter than usual until the acute onset of the present illness, which occurred a month before admission and was characterized by strange actions: she was unkind to her dog, upset the furniture, was overactive to the extent that she bruised and injured herself, refused food and was unable to sleep.

Positive Physical Findings Since Admission (Aug. 19, 1933).—On admission the patient was extremely overactive; there was frequency of urination; owing to her continual excitement and overactivity, the skin was abraded and bruised. She was well nourished and somewhat overweight; the breasts were pendulous, and there was hirsutes of the upper lip. She suffered from chronic tonsillitis and had diphtheria in April 1934. Bronchopneumonia developed on Aug. 30, 1935.

Course.—After admission the patient's mental condition varied considerably. She was the daughter of a Japanese father and an Anglo-Saxon mother. As a child she was bashful and reticent, but became an accomplished pianist and artist; she mastered the English, German and Japanese languages. In spite of the fact that she had almost continually experienced auditory and visual hallucinations, throughout her illness had been untidy and uninterested and for months had remained in a catatonic stupor, her general behavior improved so that it was possible to allow her to go home on trial four times, the longest stay being two months. At the time of taking the first biopsy specimen the patient was uninterested and uncommunicative; she sat about the ward and was untidy in appearance, but was able to carry on an animated, coherent conversation when her mother visited her. The auditory and visual hallucinations resulted in occasional disturbed episodes.

Laboratory Findings.—The Wassermann reaction of the blood was negative, and urinalysis revealed nothing abnormal.

Operation.—On June 6, 1934, cerebral tissue was taken for biopsy in the right occipitoparietal region, to a depth of 4.5 cm. Anesthesia was induced with avertin and intranasal administration of ether. No abnormal collection of fluid was seen in the subdural space, and the subarachnoid space was shallow. The brain was under moderate tension, and the cortex appeared light yellow. The presenting convolution was wide and the adjacent sulcus shallow. About five minutes before the biopsy specimen was taken, the blood became dark as a result of anoxemia; during the actual removal of the specimen, however, it was again bright red, and the cerebral pressure was slightly, if any, less.

Histologic Observation: The nerve cells were not unusual. Hypertrophy of the astrocytes was present. The oligodendroglia cells showed extreme general swelling (*a*, *b* and *c* types) with marked vacuolation of the cytoplasm (fig. 13).

Case 13.—*Catatonic type.*

History.—E. S., a man aged 20, had onset of symptoms five months previous to admission, with more acute symptoms a few days before. He complained of

hallucinations of voices that warned him of impending danger and at times accused him of immoral practices. He was confused and disoriented and believed that sacrifices were being offered in the next room and that poisonous gas was being introduced into his room by persons practicing religious rites.

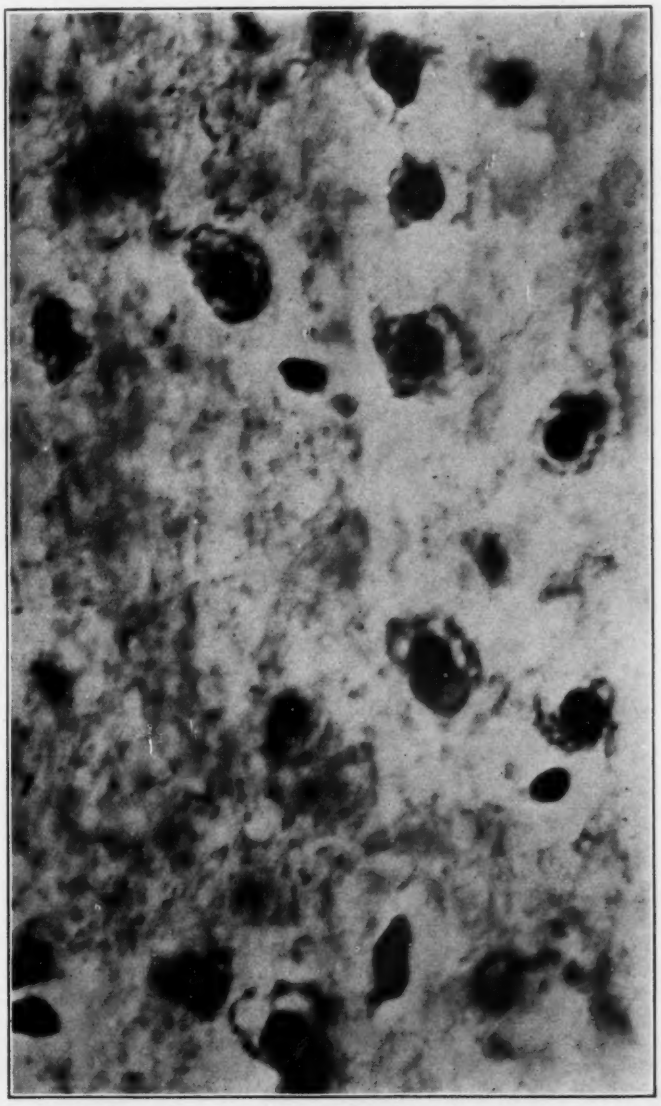

Fig. 12 (case 11).—Biopsy specimen from the right occipitoparietal region in a case of schizophrenia, of paranoid type. The specimen shows marked general swelling of the oligodendroglia cells.

Positive Physical Findings Since Admission (Nov. 17, 1933).—There was a history of appendicitis and occasional tenderness and pain in the right lower quadrant of the abdomen. The tendon reflexes were hyperactive in the upper and

lower extremities on both sides. The patient had typhoid in April 1934. There was temporary improvement in the mental condition during the period of convalescence from this illness. On the sixth day after a second specimen of cerebral tissue had been removed for biopsy, the patient had a convulsive seizure which was described as a tonic spasm of the arms and legs. He was in opisthotonos for a few minutes. Observation within a few minutes of the onset revealed that the pupils were dilated and the tendon reflexes extremely active; there was no clonus, and the abdominal responses were absent on both sides. There were plantar extension on the left and plantar flexion on the right. The

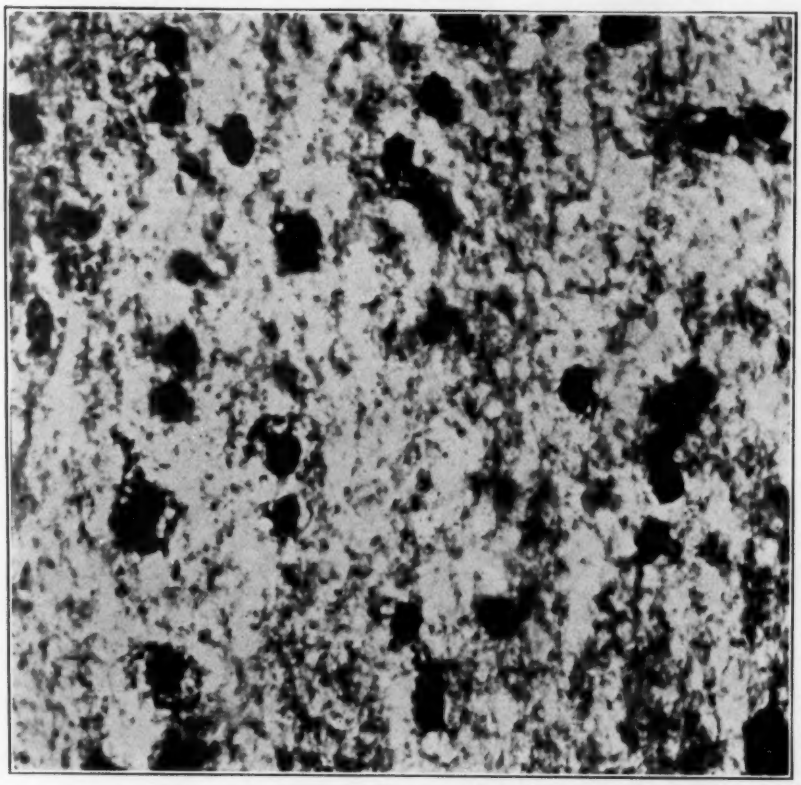

Fig. 13 (case 12).—Specimen taken for biopsy from the right occipitoparietal region in a case of schizophrenia, of catatonic type. The oligodendroglia cells show extreme general swelling.

eyegrounds were normal. There was no headache, and the pulse was rapid and bounding. After the seizure there was a slight rise in temperature.

Course.—On admission and until February 1936, the patient was retiring and negativistic; he had frequently been in catatonic stupor for days at a time, and between these episodes his conduct was preoccupied, silly, mischievous or impulsive, depending on the character of the auditory hallucinations governing the conduct. Such was his condition at the time of taking the first biopsy specimen. The patient's mental condition a month before the second operation had improved to a point that

would be called recovery from catatonic schizophrenia. Since this operation the patient has been well; he left the hospital a year ago.

Laboratory Findings.—Urinalysis showed an occasional trace of albumin. Examination of the sputum revealed no acid-fast bacilli. The Wassermann reactions of the cerebrospinal fluid and blood were negative. The Pandy reaction was negative. The blood chemistry, including the calcium, phosphorus, sugar and urea contents, was normal.

First Operation.—On March 23, 1935, cerebral tissue was taken for biopsy in the right occipitoparietal region, to a depth of from 3 to 3.5 cm. Ether was given intranasally. No subdural fluid was seen. The subarachnoid space was shallow, but when the brain was displaced deep spaces were seen. The brain was under moderate tension. The cortical surface was grayish blue—almost the color of a tumor. The presenting convolution was fairly narrow and convex. There was no increase in resistance to passage of the needle. There was difficulty with stridulant breathing some time before the biopsy specimens were taken, but for a few minutes immediately preceding the operation respiration was fairly good. The patient became cyanotic early during the anesthesia.

Histologic Observations: The nerve cells were not unusual. The astrocytes were small and sparse, with some reacting forms. The oligodendroglia cells did not appear swollen; however, they stained with a solution of gold chloride, which is unusual with the method used.

Second Operation.—Removal of cerebral tissue for biopsy was repeated in the left occipitoparietal region on April 1, 1936, to a depth of 4 cm. Ether was given intranasally. There was stridor, but not much cyanosis. No subdural fluid was observed. The brain was under moderately increased pressure, undoubtedly due to the anesthesia. The brain was of normal consistency; indeed, it felt soft and breakable.

Histologic Observations: The nerve cells and the astrocytes were not unusual. A slight amount of patchy swelling of oligodendroglia cells was present.

BIOPSIES ON CEREBRAL TISSUE OF PATIENTS WITH MANIC-DEPRESSIVE PSYCHOSIS

CASE 14.—*Depressed phase.*

History.—W. L., a man aged 23, six weeks previous to admission entered a manic phase. He became overactive and troublesome at home, spending money freely and fighting on the street; he was violent if opposed and euphoric and expressed grandiose ideas.

Positive Physical Findings Since Admission (Dec. 12, 1933).—The patient was well nourished and well developed. He had deviation of the septum and a history of several operations on the nose. The abdominal reflexes were absent on the left side. The tendon reflexes were active in the left lower extremity, while those in the right were sluggish, but present. Plantar flexion was present on both sides. The right pupil was slightly larger than the left, and the right corner of the mouth drooped slightly (the patient had a very small mouth, which affected speech). There was some muscular atrophy of the left thigh. Eight months after operation, during one week, the patient had two generalized epileptiform seizures, which lasted for only a few minutes; he became cyanosed, had a few spasms and then appeared to be himself.

Course.—The patient gradually improved in the course of two months and was allowed to go home on trial on January 6. He was readmitted on March 6, in a

state of severe depression. His physical condition was poor at this time; at the time of the operation, he had improved somewhat and was taking sufficient nourishment, although he was depressed. The state of depression began to improve in November 1934; the patient gained weight and was discharged in excellent mental and physical condition on Jan. 5, 1935. He was seen on Dec. 30, 1935; although he was at that time in a hypomanic phase, he had been able to carry on at home.

Laboratory Findings.—Urinalysis showed an occasional trace of albumin. The Wassermann reaction of the blood was negative.

Operation.—Cerebral tissue was taken for biopsy in the right occipitoparietal region, to a depth of 4.5 cm. The anesthetic was avertin. There was no increase of subdural fluid. The subarachnoid space was normal. The cortex was of normal appearance, and the sulci were of normal depth. The brain was slightly resistant to the needle.

Histologic Observations: Many nerve cells showed pyknosis. The astrocytes, at least in the deeper layers of the white matter, had heavier, longer and more finely wavy processes than normal. In the deepest layers they were hypertrophied. The oligodendroglia cells were sparsely scattered, with irregularly spaced grouping of markedly swollen cells (*a*, *b* and *c* types), with pyknotic, angulated, black-staining, shriveled nuclei. The maximum change was observed at a depth of 1 cm., but similar changes were present throughout most of the specimen. All degrees of swelling were present. The pyknotic nuclei were surrounded with little or no, or abundant swollen vacuolated, cytoplasm (fig. 14). Close to an area of marked swelling was one of astrocytic gliosis.

CASE 15.—*Depressed phase.*

History.—R. T., a woman aged 40, had a short period of psychotic excitement, associated with a goiter, at the age of 18 years. A depressed attack occurred in 1924, from which the patient recovered after ten months in a hospital. A hypomanic attack occurred late in 1933, and she was admitted to the hospital in February 1934, in an acute episode.

Positive Physical Findings Since Last Admission (Feb. 24, 1934).—Previous to admission the patient had swallowed a number of foreign bodies, including needles and pins, for suicidal purposes. These were demonstrated by roentgenograms. In May, 1934, the patient was acutely ill because one of the foreign bodies had perforated the intestine; however, recovery was uneventful. On March 16, 1934, she attempted suicide by cutting her wrist; hemorrhage was severe, and she had one epileptiform seizure while the wound was being sutured, with the area under local anesthesia. Recovery was uneventful. A convergent squint, due to weakness of the right lateral rectus muscle, dated from an attack of measles at the age of 7 years. Sense of smell was diminished on the right; the Weber and Rinne tests gave normal results, but hearing was slightly defective. The patient had had an injury to the head several years before which was followed by unconsciousness for a short time. She had an attack of pneumonia prior to her admission in 1934.

Course.—On admission and until the specimen was taken for biopsy, the patient was depressed and agitated. She appeared to improve somewhat after the operation. Tonsillectomy was done in July 1934, and varicose veins were treated by injection in November. The patient was discharged on trial in good condition on December 8. Attempts were made in the spring of 1935 to have the patient return for removal of a second biopsy specimen; it was noted at this time that the psychosis was in a hypomanic phase. The patient returned to the hospital in June 1935, in an extremely depressed state and has remained so until the present.

Laboratory Findings.—Urinalysis showed an occasional trace of albumin, and the Wassermann reaction of the blood was negative.

Operation.—On June 14, 1934, cerebral tissue was taken for biopsy in the right occipitoparietal region, to a depth of 4.5 cm. Ether was used intranasally, with 1/150 grain (0.4 mg.) of atropine sulfate. No fluid escaped from the subdural space and little from the subarachnoid space. The brain was under moderate pressure. Its surface was yellowish white. On first puncture the biopsy needle encountered definite increase in resistance in the outer layers, then apparently normal resistance in the next layer and greater resistance in the deeper layer. On

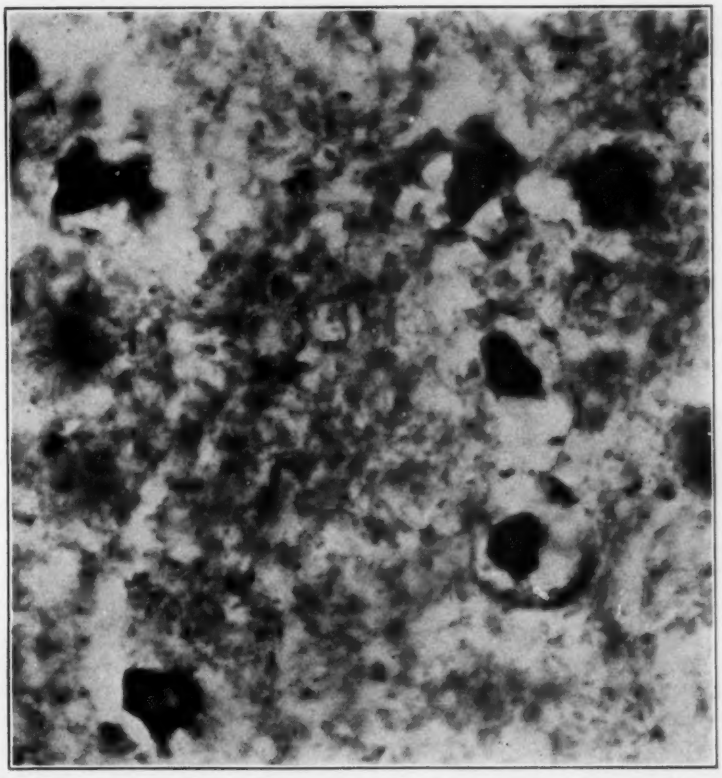

Fig. 14 (case 14).—Specimen taken for biopsy from the right occipitoparietal region in a case of the depressed phase of manic-depressive psychosis. The picture shows an extreme degree of cytoplasmic vacuolation, with pyknosis and angulation of the nuclei.

second puncture the superficial layers seemed softer, possibly owing to passage of the first needle, but in the middle and deep layers the brain tissue became somewhat more resistant.

Histologic Observations: The nerve cells appeared normal. The astrocytes varied from normal to mildly hypertrophic. There was marked swelling (*a* and *b* types) of oligodendroglia cells.

CASE 16.—*Manic (mixed) type.*

History.—V. T., a woman aged 24, a few days prior to admission became anxious, agitated and apprehensive and feared that she was going to injure herself.

There were secondary delusions in keeping with the expression that "her bones were broken and there was no blood in her veins."

Positive Physical Findings Since Admission (Nov. 16, 1934).—Appendectomy had been performed several years previous to admission; otherwise, the patient's physical condition was and has been excellent. It was noted that the patient had marked vasomotor reactions in keeping with her emotional reaction; that is, she became pale when angry and flushed when happy and excited.

Course.—On admission the patient was depressed; since, she has been in a state of acute psychosis characterized by emotional instability and overactivity, which persisted at the time of removal of both biopsy specimens. During the greater part of the time she was in a state of extreme euphoria and, this being considered, in good contact with reality; however, this state was interrupted by short periods of irritability, when she was extremely agitated, impulsive and violent. The manic-depressive features more than outweighed the few symptoms that suggested schizophrenia. There has been no evidence of deterioration up to the present.

Laboratory Findings.—Urinalysis showed an occasional trace of albumin.

First Operation.—On March 4, 1935, cerebral tissue was taken for biopsy in the right occipitoparietal region, to a depth of 3.5 cm. Ether was used intranasally, supported by ¼ grain (0.016 Gm.) of morphine sulfate and 1/150 grain (0.4 mg.) of atropine sulfate. There was no subdural fluid. The brain bulged into the opening in the bone, obliterating the subarachnoid space, which may have been larger than could be seen. The cortical surface was grayish yellow—more grayish than the cortex in case 19. The brain felt slightly gliosed; at a depth of 3 cm. this became definite. The specimen removed was more grayish than usual. The site of removal did not stay open as markedly as that in case 19.

Histologic Observations: Many nerve cells showed pyknosis, which may have been an artefact. The astrocytes were large, rather numerous and regularly spaced and showed slight hypertrophy with long processes. The oligodendroglia cells had large nuclei and were moderately swollen (*a* and *b* types). Weigert-Pal preparations showed no evidence of degeneration in the visible white matter, and fat stains revealed nothing unusual.

Second Operation.—A second specimen for biopsy was taken on April 29, 1936, in the left occipitoparietal region, to a depth of 4.5 cm. Ether was used intranasally, with smooth results. There was no collection of subdural fluid. The pia mater showed increased toughness, and the brain was under moderate pressure. A certain amount of resistance to the needle was felt, but this was not as evident with the second puncture.

Histologic Observations: The nerve cells appeared normal. The astrocytes were not stained specifically, but swelling of the oligodendroglia cells (*a* and *b* types) was fairly marked.

CASE 17.—*Manic phase.*

History.—D. R., a woman aged 24, had a manic attack, of two months' duration, in 1928, and the onset of the present attack was three weeks prior to admission. The patient was excitable and irritable, kept the household awake the greater part of the night, was abusive to her husband and friends, quarreled and was violent and destructive.

Positive Physical Findings Since Admission (March 30, 1934).—The patient's physical condition was excellent. A soft systolic murmur was heard over the apex of the heart.

Course.—On admission and up to the time of taking the biopsy specimen, the patient presented a picture of acute mania without schizophrenic features. She was elated and erotic and showed marked motor excitement, flight of ideas, momentary periods of irritation and occasional paranoid ideas. After the operation she improved rapidly and was discharged on June 31, 1935; she was still hypomanic, but has remained at home since.

Laboratory Findings.—Urinalysis revealed nothing abnormal, and the Wassermann reaction of the blood was negative.

Operation.—On May 16, 1934, cerebral tissue was removed for biopsy in the right occipitoparietal region, to a depth of 4.5 cm.; ether was used intranasally. The brain was under moderate pressure. There was no collection of subdural fluid. Only a small amount of cerebrospinal fluid escaped when the brain tissue was displaced. (The patient was dehydrated.) The pia-arachnoid was of normal appearance. The surface of the cortex was slightly grayish, which was probably normal. The presenting convolution was wide; a sulcus was not seen. (There had been difficulty in administration of the anesthetic, which caused cyanosis and shallow breathing earlier in the operation, but at least ten minutes before and during taking of the specimen the patient's color had been satisfactory.) On the first puncture the outer layers felt somewhat resistant; the central strata were normal or soft; increased resistance was noted at a greater depth, as in case 15. On the second puncture, no unusual resistance was noted. The patient soon improved after the operation and returned home.

Histologic Observations: The nerve cells showed pyknosis, which was probably an artefact. The astrocytes displayed chronic gliosis. The oligodendroglia cells showed marked swelling (*a, b* and *c* types).

CASE 18.—*Schizoid type.*

History.—D. C., a woman aged 24, began to have acute symptoms about four weeks previous to admission, with depression, feelings of insufficiency and fear of pregnancy. She became agitated, had episodes of screaming and attempted suicide. The patient's father had committed suicide. A sister had become psychotic during the puerperium; this appeared to be a large factor in the patient's fear of pregnancy.

Positive Physical Findings Since Admission (May 25, 1933).—The patient was poorly developed and undernourished on admission. She was of asthenic, dysplastic type, with hirsutism over the face and extremities, but otherwise was in good physical condition.

Course.—Although the patient was depressed on admission, many of the delusions that she expressed appeared to be bizarre; there had always been a somewhat rigid emotional reaction. "My heart has left my body; I have no blood; people are influencing my thoughts and actions"; consequently, she was impulsive and violent. At times she was mute and negativistic. For many months the condition was considered to be catatonic schizophrenia. The more disturbed episodes were of short duration; with time it became apparent that usually the patient could converse well on any subject except her personal experiences; at no time was it possible to obtain from her the important elements which were obviously present. Such was her condition at the time of removal of the biopsy specimen. The operation did not appear to affect her conduct in any way. On April 16, 1934, she was put to bed, complaining of nausea and headache. On examination it was observed that the tendon reflexes were extremely active, slightly more so on the left. The knee and the ankle clonus were exhaustible

in both lower extremities. Recovery was uneventful. The patient began to improve three years after admission, coincident with the administration of an estrogenic substance (emmenin) and a gonadotropic substance from the placenta (prepared by the method of Collip). Improvement was gradual. The general appearance improved, although she did not gain weight. She was allowed to go home on trial on April 19, 1935; improvement continued, and she remains well. Another sister has since been admitted to the hospital in a state of acute agitated depression.

Laboratory Findings.—Urinalysis showed an occasional trace of albumin. The Wassermann reaction of the blood was negative, and examination of the cerebrospinal fluid revealed nothing abnormal. The Pandy reaction, the colloidal gold curve and the cell count were normal.

Operation.—On March 21, 1934, cerebral tissue was removed for biopsy in the right occipitoparietal region to a depth of 4 cm. Anesthesia was induced with avertin and intranasal administration of ether. The scalp was unusually vascular. The brain bulged into the burr opening under high pressure, probably as a result of the anesthetic. The cortex appeared fairly normal and light yellow. A neighboring sulcus was shallow.

Histologic Observations: The architectonic and nerve cells of the cortex were normal. The astrocytes were sparse, with small, short and twisted processes; in some areas they were sparse with chronic swelling or hypertrophy, and in others, more numerous with marked swelling or hypertrophy. The oligodendroglia cells were numerous and small. Slight swelling was present. There were areas in which the nuclei were pyknotic and others in which they were round.

BIOPSY ON CEREBRAL TISSUE OF A PATIENT WITH AN UNCLASSIFIED PSYCHOSIS

CASE 19.—*Encephalitis, type unknown.*

History.—I. W., a woman aged 30, became ill suddenly. She was living in the country, recuperating from physical and mental shock, her husband having beaten her two months before and then deserted her. Five days before admission she felt "queer," telephoned her mother by long distance and remembered nothing then until she was well on the road to recovery, several months later. For the few days prior to admission she was delirious, extremely overactive, profane, violent and destructive.

Positive Physical Findings Since Admission (Dec. 19, 1934).—On admission the patient was dehydrated and extremely agitated; the breath smelled of acetone. There was a profuse vaginal discharge. Examination of the nervous system was difficult, but revealed plantar extension bilaterally. The pulse rate was 120, and the temperature 102 F.; the patient was flushed. There were bruises on the arms and legs. The motor restlessness was so extreme that it was difficult to differentiate between choreiform and purposeful movements. The motor excitement and extensor plantar responses were not improved for three and one-half months; then gradual improvement began, and on April 15, although the tendon reflexes were exaggerated, the plantar response was of flexor type. For the first month of illness the temperature ranged from 103 to 99 F.; during the second and third months it was usually below 100 F., and after this it remained normal.

Course.—During the first week in the hospital the patient appeared to be completely unaware of what was going on around her. She talked continually;

some of her productions suggested auditory hallucinations and perseveration. Neither true automatic activity nor negativism was observed: "Hell, wants to break my will power"; "will spit it out in your face"; "stop singing, stop singing, stop, stop, no, no, no." The patient's excitement was so severe that it was necessary to give repeated large doses of the following sedatives to prevent exhaustion: pentobarbital sodium, paraldehyde, scopolamine and apomorphine hydrochloride. The restlessness was so extreme that even when the patient was unconscious and comparatively quiet there were continuous flexor movements of the fingers bilaterally. The patient's physical condition was maintained for three months with tube feeding, intravenous and subcutaneous injections of dextrose and saline solution, enemas and catheterization. With this care, the patient's physical condition improved, and at the time of taking the biopsy specimen the temperature was occasionally normal and only occasionally above 100 F. During the fourth month of illness the patient began to improve gradually; the improvement could scarcely be noticed over a few days, but was progressive from week to week; she was discharged as apparently well on May 3, five months after the onset.

Laboratory Findings.—Repeated Wassermann tests of the blood and spinal fluid gave negative reactions. The Pandy test repeatedly gave normal results, as well as the cell counts of the blood and spinal fluid.

Operation.—On Feb. 25, 1935, cerebral tissue was taken for biopsy in the right occipitoparietal region, to a depth of 3.5 cm. Ether was used intranasally, with ¼ grain (0.016 Gm.) of morphine sulfate and 1/150 grain (0.4 mg.) of atropine sulfate. The brain was under normal pressure. Nothing abnormal was noted in the subdural space. The subarachnoid space did not appear deep; actually, however, the convolutions were round, and the sulci, deep. The surface of the cortex was yellowish gray, especially yellow. It appeared to have undergone gliosis. In taking the first specimen the cortex felt more resistant than normal, thus showing definite gliosis; this resistance became more marked in the deeper layers. When the hollow needle was withdrawn, the hole in the brain gaped widely—the third evidence of cerebral gliosis in this case.

Histologic Observations: Occasional nerve cells appeared to be degenerated, with increased satellitosis. The astrocytes were sparse and of normal appearance; occasionally there was a slight reaction. The oligodendroglia cells showed moderate swelling (*a* and *b*), which in some patchy areas was more marked (*a*, *b* and *c*).

COMMENT

There can be little doubt that a pathologic change affecting the oligodendroglia cells of the brain operates in cases of schizophrenia and manic-depressive psychosis. The cells present the appearance of so-called acute swelling. Removal of a second specimen for biopsy from the same patient, even after an interval of one or two years, has shown that the effect on the appearance of these cells is relatively little changed in the long interval (figs. 5 *A* and *B*, 6, 7 and 8). It is hardly possible to say with assurance that the same cell lives in a state of swelling for a year, but as most cells in the specimens are affected, it is logical to admit the probability that the change is chronic rather than acute; at all events, the process may be chronic as well as acute.

Two types of swelling seem to be possible (fig. 1). On the one hand, the nuclei approach the normal (figs. 11, 12 and 13), and, on the other,

they are markedly pyknotic (figs. 5 *B*, 9, 10 and 14). One cannot be certain at present of the significance of the two types of swelling of the oligodendroglia cells, owing to the difficulty both of psychiatric classification and of histologic appraisal; on the other hand, their importance is obvious.

No essential or constant difference is found in the present analysis between the changes in patients with dementia praecox and those in patients with manic-depressive psychosis. The change was seen to a marked degree in all but 3 of the 19 patients with psychoses. In one of the 3 (case 18), whose disease was classed as manic-depressive psychosis of schizoid type, slight swelling could, nevertheless, be seen. Sections also gave the impression of an apparent increase in the number of oligodendroglia cells, with patchy areas in which their nuclei appeared to be increased in number and pyknotic. In addition, small sparsely scattered astrocytes showed short thick twisted processes and, in some areas, swelling or hypertrophy. In the second exception (case 13), the disease was classified as the catatonic type of schizophrenia. Specimens were removed for biopsy on two occasions. In the first specimen, obtained from the right occipitoparietal region, nothing definitely abnormal was observed in the oligodendroglia cells, although it is interesting that they were stained with a solution of gold chloride. Some changes were present in the astrocytes, which were small and sparsely scattered. On removal of a second specimen for biopsy a year later from the opposite, left occipitoparietal region, however, mild first degree swelling, of patchy distribution, was observed.

The third patient (case 3) had a disease classified, with some doubt, as deteriorated schizophrenia. Two operations were performed. In the first specimen, taken from the right occipitoparietal region, the oligodendroglia cells were few, but of normal appearance (fig. 7). An area of moderate astrocytic hypertrophy was seen. In the second biopsy specimen, taken a year later from the right frontal region, questionable, if any, swelling was present (fig. 8). The astrocytes appeared normal. This was the only patient in the present series with no obvious abnormality of the oligodendroglia cells. In this patient, on the other hand, gross abnormalities were noted at operation, particularly with regard to the meninges, and an unusual number of pyknotic ganglion cells was observed in the first specimen. The clinical diagnosis was not entirely clear; psychiatrists hesitated whether to classify the condition as feeblemindedness or schizophrenia. Pathologically, one may conclude that the patient was suffering from a degenerative lesion.

It is of interest that 2 of the 16 patients used as controls from whom specimens for biopsy were taken during status epilepticus and who had disturbance of mentality between attacks showed swelling of oligoden-

droglia cells (W. E. [fig. 2] and P. S.), whereas a third patient with intervals of clear mentality between seizures showed none (A. S. [fig. 4]). Furthermore, swelling was noted in a specimen obtained during exploratory craniotomy at the time of an attack in a patient suffering from epilepsy. Mild swelling of the oligodendroglia cells was reported by Penfield and Cone in the case of a patient suffering from an average of thirty epileptic seizures a day. The patient was drowsy, but otherwise mentally clear. It may again be stated that in patients who are mentally normal, and in the absence of epileptic seizures, swelling of oligodendroglia cells is not seen provided there is not an inflammatory or degenerative process in the neighborhood. Normal laboratory animals do not show swelling of the oligodendroglia cells.

The change in the oligodendroglia cells observed in psychotic patients may occur at any depth in the white matter between the gray matter of the cortex and the ventricle. It is perhaps more prominent at a depth of 1 cm. and in the deeper layers. It may be patchy or generalized. It does not occur to any extent, if at all, in the gray matter.

In addition to the changes in the oligodendroglia cells, there is in the majority of cases evidence of slight astrocytic reaction.

It is already known from the work of Penfield and Cone that acute swelling of oligodendroglia cells occurs in a variety of conditions associated with mental derangement. It was observed for the most part in postmortem material, and to a marked degree when death had been preceded by a protracted period of stupor or coma. It was observed in a specimen taken from a living patient suffering from repeated epileptic seizures and in another after cerebral embolism. Penfield and Cone also reported swelling of oligodendroglia cells as a result of experimental intoxication in animals. Confirmation of much of this work has been reported in the Italian literature (Cardona,[8] Roberti[9] and Bolsi[10]).

Swelling of oligodendroglia cells is frequent in states associated with coma or stupor. It is of interest, therefore, that psychotic patients also

8. Cardona, F.: Sul rigonfiamento acúto della oligodendroglia e microglia, e sulla "clasmatodendrosi" della macroglia nell'uomo, Riv. di pat. nerv. **38**:906-915, 1931; footnote 4.

9. Roberti, C. E.: Sul comportamento della macroglia e degli elementi nervosi nelle intossicazioni sperimentali da: istammina, guanidina, acido cloridrico, acetato di piombo e acetato talloso, Rassegna di studi psichiat. **20**:7-29, 1931; Contributo allo studio del comportamento della nevroglia e degli elementi nervosi nelle sindromi mentali tossiche (amenza e demenza precoce iniziale) ibid, **20**: 30-56, 1931; Contributo allo studio della microglia nei malati di mente (amenti e dementi precoce), Riv. di pat. nerv. **38**:461-482, 1931.

10. Bolsi, D.: Ricerche sulla microglia e la oligodendroglia: Alterazioni degenerative, Riv. di pat. nerv. **37**:1-13, 1931.

show similar changes in the oligodendroglia cells, which as a rule are of marked degree.

The change in the oligodendroglia cells is striking, and there can be little doubt as to its importance. These cells behave like sensitive indicators. They react quickly to abnormal influences on the central nervous system. Since the phenomenon is observed principally in the white matter in psychotic patients and the oligodendroglia cells parallel the white fiber pathways, one wonders whether the neighboring conducting axons are directly or indirectly affected in the same process. It is conceivable that such a condition may interfere with the passage of associative impulses from one portion of the brain to another and thus disrupt thought processes.

SUMMARY AND CONCLUSIONS

1. Schizophrenic and manic-depressive psychoses are associated with demonstrable histologic changes in the brain.

2. Swelling of the oligodendroglia cells occurs in association with schizophrenia and manic-depressive psychosis. There is often accompanying mild hypertrophy of the astrocytes.

3. Two main types of oligodendroglial change are described: (*n*) that in which the nuclei are normal, and (*p*) that in which they are pyknotic (fig. 1).

4. Swelling of oligodendroglia cells evidently can occur as a chronic process. It has been observed on second biopsy of cerebral tissue at the end of one, or even two, years.

5. Swelling of oligodendroglia cells was observed in 2 patients with status epilepticus who were mentally confused between seizures. It was not present in the brain of a patient with status epilepticus who was mentally clear between seizures. It existed in 1 patient at the time of an epileptic seizure.

6. The change in the oligodendroglia cells in psychotic patients occurs in the white matter. It may be general or patchy in distribution. At a depth of 1 cm. and in the deeper layers it is often more intense.

7. In view of the changes in the oligodendroglia cells, it is suggested that the mental phenomena are associated with massive physiologic disturbances in associational and commissural fiber pathways in the brain. In this way, impulses from different parts of the brain are interrupted, with consequent disturbance and loss of control in the intellectual, volitional and emotional fields.

8. By analogy with the other states in which swelling of oligodendroglia cells is observed, it is justifiable to assume that in psychotic states also there may be a causal toxic or metabolic factor.

DISCUSSION

DR. ADOLF MEYER, Baltimore: It is fortunate that a study has been made that will circumvent to some extent the usual belief that one is dealing with conditions that have already been altered and are modified by the length of time between death and the fixation of the tissue and examination in the laboratory. It is particularly impressive to me, and is to be commented on with a great deal of emphasis and satisfaction, that the presentation has frankly concerned one element of observation. On the other hand, however, there is perhaps too definite a statement of one word, "diagnosis"—the kind of thing perhaps of which most neurologists have become suspicious, because they deal with complex data. This is mitigated by the fact that the investigators report disturbances practically everywhere without claiming that they have found a distinction that will satisfy the often fatal desire to fit the observations to the one word "diagnosis." The presentation is a frank statement that the disturbances occur in various degrees, as designated by various clinical terms.

The impression that I get is this: Before one considers items that must be specific and unique and before one makes too sweeping and simple a generalization to satisfy the old craving for classification, it is important to keep centers of attention and concern well defined and to leave the items where they are observed. That one is dealing with what is observed concerning one element under a variety of conditions ought to be borne in mind and will, I think, be fruitful; but the observations will have to be combined with an equally specific knowledge of other conditions. So far, the changes in the oligodendroglia cells are too uniform and occur under too many conditions to seduce one into drawing rash conclusions.

Hence my reaction is this: I wish to express my sincere compliments to the authors for a presentation which focuses itself on something that is relatively limited and that will have to find its place; on the other hand, I wish to express my belief that it is unfortunate that the terminology that is used for the conditions under which it was obtained still leaves varied, and not unequivocal, the identification of the lesion with specific clinical conditions.

DR. ARMANDO FERRARO, New York: The interesting facts that Dr. Elvidge and his co-worker have presented concerning the existence of organic changes in so-called functional psychoses are gratifying, as they seem to lend support to the conception that a few investigators have held as to the existence in the group of functional disease of a subgroup in which definite organic changes are present. One cannot escape the fact that the swelling of the oligodendroglia cells is either a normal feature in a normal brain or the expression of a real pathologic process. Because of the fact that one is accustomed to correlate acute swelling of the oligodendroglia cells with toxic processes in general, this seems to be a point in favor of the possibility that certain functional psychoses may be associated with changes in the central nervous system of a definite organic nature.

Whether these changes are primary, that is, the expression of the primary toxic agent, or whether they are secondary, that is, the expression of changes resulting from organic imbalance accompanying psychogenic stimuli, is another question. I have always believed that in cases of mental disease one may be dealing with three main groups: In one group, the psychogenic stimuli are primarily at work, and the cessation of these stimuli will result in recovery from the mental condition. In another, psychogenic factors may be active at the onset of the mental condition but may produce indirectly, through vegetative or somatic imbalance, definite organic changes. In this group, once the psychogenic factors have ceased to operate, the organic changes may remain as an expression of the damage produced by the

primary psychogenic factors. In a third group, that of the so-called organic conditions, definite organic etiologic factors can be established as the basis of organic pathologic changes. The acute swelling of the oligodendroglia cells reported by the investigators is, therefore, likely to fall into one of the last two groups, representing possibly either the organic changes resulting from a primary psychogenic stimulus or a primary organic change produced by a primary toxic factor.

Dr. L. H. Cornwall, New York: In order to clarify one or two points in my mind, I wish to ask two questions. They do not necessarily pertain to this presentation. At a former session, I think Dr. Penfield made the remark that he had never seen changes in the oligodendroglia cells without concomitant clinical evidence of alteration of consciousness. If I am quoting him inaccurately, I hope that he will correct me.

My conception and that, I think, which most of the members have obtained from the work of Dr. Penfield and others is that the changes in the oligodendroglia cells are the first to occur in any pathologic alteration of the central nervous system. I ask whether it is possible to reconcile this attitude with Dr. Penfield's statement that alterations in the oligodendroglia cells are always accompanied by clinical evidence of alteration of consciousness, since it is a familiar clinical situation to note definite evidence of neural lesions without any gross disturbance of consciousness. My second question is this: Is it known that presumably normal brain tissue is always free from the changes in the oligodendroglia cells which are now considered to be pathologic alterations?

Dr. S. Bernard Wortis, New York: It appears to me that one tries to draw too clear a line between functional and organic psychiatric conditions. The charts that Dr. Elvidge showed impressed me as indicating that this reaction of the oligodendroglia was present in all the specimens from psychotic patients examined, irrespective of the type of mental aberration. I wonder whether Dr. Elvidge has attempted to make any metabolic studies of the tissue in the living state. Many aberrations in the metabolism of the brain tissue do not show themselves when the tissue is studied histopathologically. The histopathologic technic has definite limitations, and it seems to me, in view of this fact, that studies along metabolic lines may give additional information and perhaps make it possible to differentiate biochemically some of the tissue reactions that Dr. Elvidge has so well demonstrated in dead tissue.

Dr. Lawrence S. Kubie, New York: I wish to make one point with regard to the interpretation of these observations. First, it is well known that the changes in the oligodendroglia cells are among the most reversible that the pathologist has recognized. Second, oligodendroglia elements are extremely sensitive to changes in the body metabolism. It is recognized that in any severe mental disturbance serious upsets may occur in nitrogen metabolism, endocrine balance, distribution of fat and fluids, vasomotor control, etc. No one can say, however, whether such changes are primary and causal or secondary to emotional forces operating through the vegetative nervous system. Obviously, then, the sensitive oligodendroglia cells may serve as indicators of these complex bodily changes without clarifying at all the causative relationship of the cellular changes, the chemical changes and the mental condition of the patient. How that problem will be solved is another story.

Dr. Wilder G. Penfield, Montreal, Quebec, Canada: I wish to say a word about normal oligodendroglia cells. The work Dr. Elvidge has presented is entirely his own. I have, however, seen the sections, and I should like to put on record my opinion that there is no question about the swelling of the oligo-

dendroglia cells in these cases. From the point of view of what the oligodendroglia is, there is a great deal one may say. Its cells are the most numerous in the central nervous system—I think more numerous than nerve cells, even when one includes the small cells. It has a curious structure. Its cells contain gliosomes which morphologically resemble the granules which appear in various cells of internal secretion. They look like secretory granules. They appear when myelin is first formed; they are large then and become small later.

In the normal brain acute swelling does not occur. The authors have pointed out that one perhaps must consider the change in oligodendroglia cells as a chronic rather than an acute condition under the circumstances they describe.

Dr. Cone and I for several years took every opportunity to examine normal brains of mammals: all the usual types of animals and human beings. It is rarely that a pathologist sees a normal human brain, for the oligodendroglia undergoes a change in the few hours that precede death. The first normal human cerebral tissue that we were able to observe was obtained from a man who was admitted to the hospital with brain tissue in his ear, where it had been exuded through a subjacent fracture of the skull. We mopped out the brain tissue and fixed it at once. That tissue showed no swelling of the oligodendroglia cells. There is swelling or alteration in the oligodendroglia cells of the brain in practically every case in which autopsy is performed because of the agonal change and because change takes place rapidly in these cells post mortem.

Perhaps Dr. Elvidge will allow me to answer Dr. Cornwall's question about the significance of swelling, for the question was prompted by my statement yesterday that I had never seen marked acute swelling in the oligodendroglia cells when there was not some disturbance in the consciousness of the person from whom the tissue came. I referred to properly taken material not to that taken at necropsy. The oligodendroglia cells of the patient who dies in the hospital in coma (as such patients usually do) always show some change, but in properly taken material my co-workers and I have never seen swelling when there was not disturbance of consciousness in some form. I realize that "disturbance of consciousness" is open to interpretation.

On the other hand, in all cases of toxic delirium associated with febrile illness—the delirium or stupor, for instance, produced by abnormal processes outside the brain—acute swelling of the oligodendroglia cells is present. In such cases it is the only pathologic change that one can demonstrate within the brain.

The next point is the significance of Dr. Elvidge's observations for mentally disturbed persons. Oligodendroglial change means that an influence is at work that may be called toxic. In my opinion, it indicates that the cause of the disturbance is outside the central nervous system only because it is usually seen in patients for whom this is obviously true. It is known, as Dr. Kubie pointed out, that oligodendroglial change is a reversible process. This suggests that removal of the toxic process (whatever it is and whether it is inside or outside the cranial cavity) would allow the brain to return to normal as far as pathologic changes are concerned.

Dr. Arthur R. Elvidge: I wish to thank Dr. Meyer for his wise counsel and valuable suggestions. When my co-workers and I first did this work it was my impression that the oligodendroglial change must be an artefact; on studying the specimens used as controls, however, one is forced to believe that the change is real, and to realize that the oligodendroglia cells are simply acting as indicators. Even though the clinical diagnoses may be variable, as indicators the oligodendroglia cells, I think, may give a positive reaction in the whole group, or in a certain number, of cases.

With regard to Dr. Ferraro's question as to whether the effect is primary or secondary: One cannot say at the moment, but it would be of considerable interest to find out; perhaps one might derive some light by studying patients in the early stages of schizophrenia or manic-depressive psychosis. We intend to look for patients of this type.

Dr. Penfield has already answered Dr. Cornwall's questions. Dr. Penfield's statement that the oligodendroglia cells are perhaps the most sensitive indicators in the central nervous system is verified in the present cases, for one finds practically no change in the astrocytes. I have not mentioned the astrocytes because there was not time. In some cases they show mild hypertrophy or are smaller than normal, with thicker processes, but the change is so slight that one can hardly be definite.

One cannot be sure that nerve cells change greatly. They show changes, but I, personally, believe that these are artefacts.

With regard to Dr. Wortis' question: I believe that metabolic studies, if they could be carried out, would be of great value. Histologic methods are limited, but one has the control cases for comparison. I think that Dr. Wortis' suggestions are valuable; chemical studies should certainly be made.

As to Dr. Kubie's remarks concerning the reversibility of the reaction of the oligodendroglia cells in the brain, in which my co-workers and I have always believed: It is, I think, of interest that the oligodendroglia cells in our patients showed practically the same state of swelling at the taking of a second biopsy specimen, twelve months after removal of the first. This makes one wonder whether or not the change is reversible, for the patients improved clinically, with remissions, and the condition of 1 patient with encephalitis apparently returned to normal, although we do not know the condition of the oligodendroglia. In any case, the oligodendroglia apparently can stay in the same state for a year.

I believe that the oligodendroglia cells act simply as indicators. The real action may be exerted on the white fiber pathways, diffusely throughout the brain, for the oligodendroglia cells line these pathways. If the oligodendroglia cells are the more sensitive indicators, probably the same toxin is affecting the white fibers, because the oligodendroglia cells in the gray cortex do not swell to any extent. I believe, therefore, that the white fibers may be physiologically altered (the specimens are small, and one cannot judge adequately mild changes in the Weigert-Pal preparations in any case), so that one does not necessarily see any anatomic change in the section. In these circumstances, if one may look at it in a fantastic way, the patient's thoughts may be interrupted or split up, as it were, from one portion of the cortex to another, and the communication between parts may be completely upset.

SWEAT SECRETION IN MAN

III. CLINICAL OBSERVATIONS ON SWEATING PRODUCED BY PILOCARPINE AND MECHOLYL

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AND

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In spite of considerable clinical and experimental work, the physiologic activities involved in sweating produced by pilocarpine and mecholyl (acetylbetamethylcholine hydrochloride) are not completely understood. In 1931 Cushing [1] suggested that pilocarpine may act centrally on a parasympathetic center in the diencephalon. He produced in man by intraventricular injection of pilocarpine (and also of extract of posterior pituitary) generalized vasodilation, sweating, decrease in temperature, salivation and vomiting. This reaction was not obtained in patients in whom the hypothalamic area was destroyed (by tumor).

Cushing's statement was not in agreement with the experience of previous investigators, who maintained that pilocarpine when administered subcutaneously had a peripheral point of attack. Langley,[2] Langley and Anderson,[3] Burn [4] and Wilson [5] assumed that pilocarpine acted directly on the sweat glands. These authors supported their view by the fact that the response to pilocarpine is preserved after degeneration of the postganglionic sympathetic fibers, which represent the only anatomically established nerve supply for the sweat glands. Furthermore, Langley and Anderson [3] found that after complete degeneration of mixed peripheral nerves the sweat secretion of cats is retained in

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1. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield Ill., Charles C. Thomas, Publisher, 1932, pp. 55-106.

2. Langley, J. N.: The Secretion of Sweat: I. Supposed Inhibitory Nerve Fibres in the Posterior Nerve Roots; Secretion After Denervation, J. Physiol. **56**: 110-119, 1922.

3. Langley, J. N., and Anderson, H. K.: On Autogenic Regeneration in the Nerves of the Limbs, J. Physiol. **31**:418-428, 1904.

4. Burn, J. H.: (*a*) The Relation of Nerve-Supply and Blood Flow to Sweating Produced by Pilocarpine, J. Physiol. **56**:232-247, 1922; (*b*) The Secretion of Sweat and Vaso-Dilatation Produced by Pilocarpine, ibid. **60**:365-378, 1925.

5. Wilson, W. C.: Some Aspects of the Sweat Secretion in Man, with Special Reference to the Action of Pilocarpine, Brain **57**:422-442, 1934.

the denervated areas, although it is markedly reduced. This diminution of sweating after degeneration of mixed peripheral nerves is attributed to the vasomotor changes accompanying the motor paralysis (Burn [4b]).

The observations on experimental animals form a striking contrast to those on man. Clinical investigators have always found complete anhidrosis in response to pilocarpine in cases of degeneration of peripheral nerves. Since this holds true not only for mixed but for sensory cutaneous nerves, the vasomotor changes associated with motor paralysis, obviously, cannot be a causative factor. Also, the statement of Schiefferdecker that sweating induced by pilocarpine depends on the vasodilator effect of the drug is incorrect and was disproved by Foerster.[6] Foerster pointed out that in cases of lesions of the peripheral nerves the vasodilator response to pilocarpine is retained whereas sweating is abolished. Thus, clinical experience suggests that pilocarpine acts on sweat nerves, while experiments on animals point to a direct action on the glands.

Most investigators have been puzzled by the fact that pilocarpine and, more recently, mecholyl, although specifically parasympathomimetic in their physiologic effects, stimulate the sweat glands which possess only a sympathetic innervation. The preservation of pilocarpine sweating after sympathectomy and its abolition after section of peripheral nerves suggest the possibility of a double innervation of the sweat glands, a fact which is established for all other vegetative organs. Although clinical (Guttmann and List [7]) and experimental evidence (Hasama [8]) supports the theory of a double innervation, anatomic proof is lacking for the existence of a direct parasympathetic nerve supply to the sweat glands. The problem of how parasympathetic fibers possibly innervate the sweat glands was elucidated by Dale [9] and others. Dale found that stimulation of parasympathetic nerves is transmitted not directly to the

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7. (*a*) Guttmann, L., and List, C. F.: Zur Topik und Pathophysiologie der Schweiss-sekretion, Ztschr. f. d. ges. Neurol. u. Psychiat. **116**:504-536, 1928 (*b*) Guttmann, L.: Die Schweiss-sekretion des Menschen in ihren Beziehungen zum Nervensystem, ibid. **135**:1-47, 1931.

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9. Dale, H. H.: Progress in Autopharmacology: II. Acetylcholine; Its Natural Occurrence and Probable Function, Bull. Johns Hopkins Hosp. **53**:312-323, 1933.

end organs but indirectly, by the release of a chemical substance at the peripheral nerve endings. This transmitter substance has properties resembling those of acetylcholine, and probably is acetylcholine. It was found that not only the cranial parasympathetic nerves but the vasodilator fibers in the spinal nerves liberate acetylcholine. Furthermore, the transmitter substance was recovered after stimulation of anatomically true sympathetic nerves (Dale and Feldberg [10]). The latter observation led to the conclusion that the thoracolumbar system contains two sets of efferent fibers with different pharmacologic and physiologic properties. These are (1) the adrenergic fibers, which can be stimulated by epinephrine and paralyzed by large doses of ergotoxine, and (2) the cholinergic fibers, which are excited by acetylcholine, pilocarpine and other parasympathomimetic drugs and are blocked by atropine. This conception has removed the main discrepancies between the anatomic and the pharmacophysiologic point of view, but much work remains to be done in regard to the distribution of the cholinergic fibers in the peripheral and sympathetic nervous systems.

In order to clarify the controversial points, the sweating reactions following the subcutaneous injection of pilocarpine and mecholyl were studied in man and compared with the results obtained by the thermoregulatory sweating test. Our purpose in these experiments was to determine (1) whether the drugs act centrally or peripherally, (2) whether the sweat glands or the nerve endings are acted on and (3) the effect of the drugs on sympathetic and parasympathetic nerves (List [11]).

In all cases the sweating response was visualized by Minor's iodine and starch method (List and Peet [12]). The clinical observations were grouped in the following sequence:

1. Sweating in normal persons induced by pilocarpine or mecholyl.
2. Influence of circulation of the blood on sweating.
3. Sweating responses associated with lesions of peripheral nerves.
4. Sweating responses associated with lesions of the sympathetic chain.
5. Sweating responses associated with lesions of the spinal cord.

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10. Dale, H. H., and Feldberg, W.: The Chemical Transmission of Secretory Impulses to the Sweat Glands of the Cat, J. Physiol. **82**:121-128, 1934.

11. List, C. F.: Studies of Sweat Secretion in Man, Univ. Hosp. Bull., Ann Arbor **2**:40, 1936.

12. List, C. F., and Peet, M. M.: Sweat Secretion in Man: I. Sweating Responses in Normal Persons, Arch. Neurol. & Psychiat. **39**:1228 (June) 1938; II. Anatomic Distribution of Sweating Disturbances Associated with Lesions of the Sympathetic Nervous System, ibid. **39**:27 (July) 1938.

CLINICAL OBSERVATIONS

1. *Sweating in Normal Persons Induced by Pilocarpine or Mecholyl.*—In normal adults subcutaneous injection of from 10 to 16 mg. of pilocarpine hydrochloride or of from 12 to 25 mg. of mecholyl produced vasodilatation and profuse sweating of the head, neck and upper part of the chest. The vasodilator response usually was more pronounced with mecholyl. Less intense perspiration was seen over the upper extremities. In many persons the perspiration of the trunk and lower extremities was often slight, or even absent. Therefore, pilocarpine and mecholyl are not suitable for sweating tests on the lower extremities; when so used, the results should be evaluated with reservations. Both drugs produce other effects, such as salivation, lacrimation and intestinal contraction, which will not be considered in this paper.

2. *Influence of Circulation of the Blood on Sweating.*—CASE 1.—Experiment A (fig. 1 *A* and *B*): A blood pressure cuff was placed around the upper part of the left arm of a healthy student and inflated to a pressure of 150 mm. of mercury, sufficient to suppress the radial pulse. This pressure was maintained for eighteen minutes. During this time sweating was produced by means of external heat, acetylsalicylic acid and drinking hot tea.

Marked perspiration occurred over both forearms and hands, but to a somewhat lesser degree over the left forearm and hand, in which the circulation was obstructed. Sweating over the two palms did not show any definite difference.

Experiment B (fig. 1 *C*): The circulation of blood in the left forearm and hand of the same student again was arrested for eighteen minutes by means of a blood pressure cuff. Shortly after application of the cuff 16 mg. of pilocarpine hydrochloride was injected subcutaneously into the right arm. Before the pilocarpine could have taken effect, some spontaneous sweating of both palms occurred. The pilocarpine then produced moderate sweating over the right forearm and hand, increasing the previous (spontaneous) perspiration of the right palmar surface. The left forearm and hand, with the arrested circulation, remained dry except for the sweating of the palm previously noted.

These two tests show that normal sweating is produced by pilocarpine only if circulation of the blood is intact. No perspiration will occur if the drug is unable to reach the periphery through the blood stream. On the other hand, thermoregulatory sweating is effected by the nervous system and is practically independent of the circulation. The slight diminution in heat sweating noted after the vascular obstruction in experiment A is probably due to the simultaneous compression and temporary anemia of the main peripheral nerve trunks, the conductivity of which was impaired, as shown by subjective paresthesias and a mild degree of motor weakness during the test. The sweating of both palms immediately after application of the pressure cuff in experiment B was caused by nervousness and had no relationship to

the administration of pilocarpine. This so-called emotional sweating also is transmitted exclusively by the nervous system.

3. *Sweating Responses Associated with Total Lesions of the Peripheral Nerves.*—I. Total degenerative lesions of the peripheral nerves, viz., those produced by surgical section, were studied. II. In addition, regional anesthesia by the injection of procaine hydrochloride afforded an opportunity to analyze the temporary complete interruption of nerve conduction without production of degenerative changes in the nerves anesthetized.

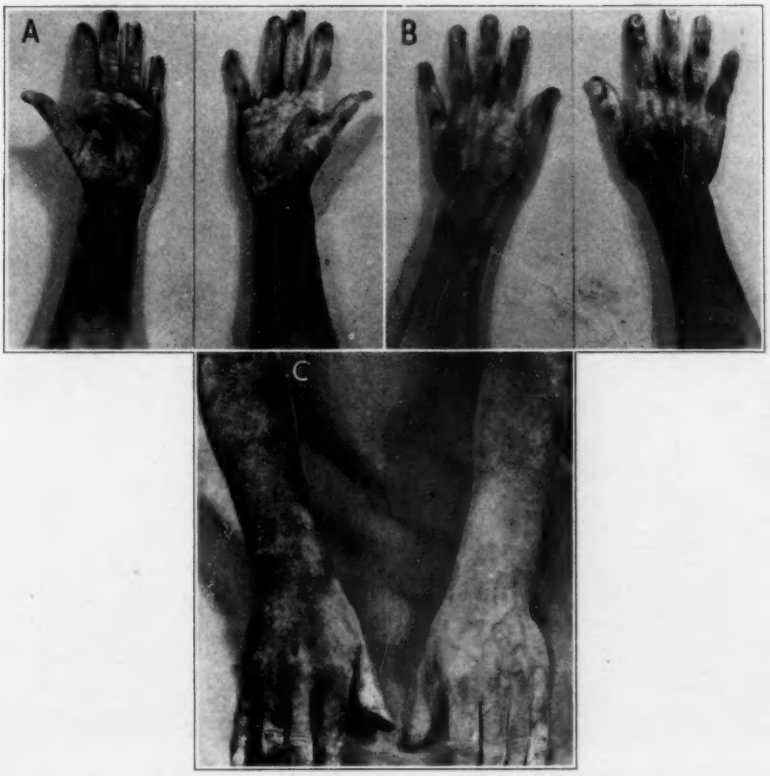

Fig. 1.—*A* and *B*, heat sweating, and *C*, pilocarpine sweating, in a normal person. The circulation of blood is obstructed in the left arm in each instance.

I. Total Lesions of Peripheral Nerves with Degenerative Changes:

CASE 2.—P. L., a student, suffered a compound fracture of the frontal bone of the skull. Both supraorbital nerves and arteries were severed. Complete anesthesia was found in the area supplied by the supraorbital nerves.

Experiment A (fig. 2*A*): A heat sweating test, fifteen days after the injury, showed anhidrosis over an area corresponding exactly to that of the sensory loss.

Experiment B (fig. 2 *B*): A pilocarpine test, sixteen days after the injury, also showed anhidrosis over an area which was slightly smaller than that produced by the heat test.

CASE 3.—A. S. suffered complete paralysis of the radial nerve following fracture of the right humerus. At operation, a large segment of the severely damaged radial nerve was resected. The gap was filled by a free graft from the lateral cutaneous nerve of the forearm.

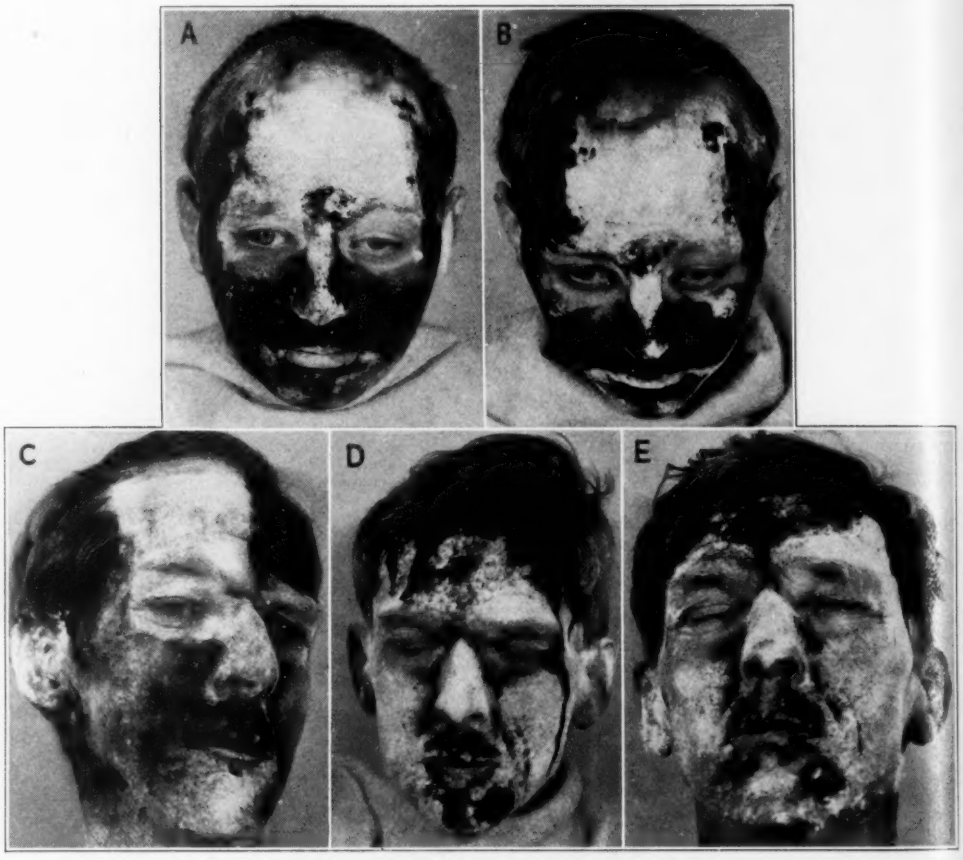

Fig. 2.—*A* and *B*, section of both supraorbital nerves. *A*, heat sweating, and *B*, pilocarpine sweating, sixteen days after the injury. *C*, heat sweating after procaine block of the right supraorbital nerve; *D*, pilocarpine sweating after block of the left supraorbital nerve, and *E*, pilocarpine sweating after procaine block of the left supraorbital and auriculotemporal nerves and the frontal branch of the facial nerve.

Experiment A: Eight days after the operation a pilocarpine test showed complete anhidrosis over the area of the sectioned lateral cutaneous nerve of the forearm.

Experiment B: On the same day mecholyl failed to produce sweating in the area of distribution of the nerve.

CASE 4.—M. S., three months before, had received a deep cut immediately above the left wrist, resulting in complete paralysis of the median and ulnar nerves.

Experiment A: Heat sweating was completely abolished in the area of sensory loss.

Experiment B: Pilocarpine produced no sweating in the area of sensory loss.

Experiment C: Mecholyl also failed to evoke perspiration in the anesthetic zone.

Complete anhidrosis in response to heat, pilocarpine and mecholyl is present after section of peripheral nerves for at least from one to two weeks. The area of anhidrosis corresponds to the area of analgesia.

II. Temporary Denervation by Block with Procaine Hydrochloride:

CASE 5.—Experiment A (fig. 2*C*): In the case of F. F., injection of procaine hydrochloride into the right supraorbital nerve induced anesthesia in the area of distribution of the nerve. The heat sweating test showed complete anhidrosis in the area of sensory loss.

Experiment B (fig. 2*D*): In the same patient anesthesia was obtained with injection of procaine hydrochloride into the left supraorbital nerve. After injection of pilocarpine, sweating occurred over the entire forehead. However, the response on the side of injection was slightly less pronounced than that on the normal right side. An observation of less importance was the occurrence of a small zone of considerable hypohidrosis over the site of the procaine depot.

Experiment C (fig. 2*E*): In the same person the supraorbital and auriculotemporal nerves and the frontal branch of the facial nerve on the left side were blocked with procaine hydrochloride. Complete anesthesia of the areas supplied by these nerves followed, with motor paralysis of the frontalis muscle and the corrugator muscle of the eyebrow on the left side. After injection of pilocarpine sweating appeared over both sides of the forehead, but was delayed and diminished on the anesthetic side.

To evaluate the result of experiment C, it must be stated that about 12 cc. of a 1 per cent solution of procaine hydrochloride containing epinephrine was injected. This amount of anesthetic distributed over a small area may have caused sufficiently intense local vasoconstriction to explain the hypohidrosis.

CASE 6.—After removal of tumors of both acoustic nerves, A. C. had complete paralysis of the seventh and eighth cranial nerves bilaterally.

Experiment A: Heat sweating was equal and normal on the two sides.

Experiment B: Injection of procaine hydrochloride into the right supraorbital nerve produced neuroparalytic vasodilatation in the area supplied by the nerve. (It was impossible to test the sensibility accurately because the patient was totally deaf and almost blind.) Injection of pilocarpine then elicited a profuse sweating response, which was equal over the two sides of the forehead.

Experiment C: Mecholyl produced a result identical with that of pilocarpine.

CASE 7.—Experiment A: The left nervus cutaneus antibrachii dorsalis and the dorsal ramus of the radial nerve of the hand of a student were blocked with procaine hydrochloride. Heat sweating in the area of sensory loss was almost nil.

Experiment B: On another day, the left nervus cutaneus antibrachii dorsalis and the dorsal branches of the radial and ulnar nerves of the same student were

blocked with procaine hydrochloride. Anesthesia was complete in the area of injection. Pilocarpine produced a moderate and equal sweating response over the extensor sides of the two forearms. The dorsa of both hands showed little perspiration, though perhaps more on the side of injection.

Temporary denervation of a cutaneous area by injection of procaine hydrochloride into the nerves supplying the region leads to total disappearance of heat sweating in the anesthetic area, provided the block is complete. The sweating produced by pilocarpine or mecholyl, however, is unchanged or only slightly diminished. This holds true for the face as well as the upper extremity. Section of the seventh nerve combined with procaine block of the supraorbital nerve or procaine block

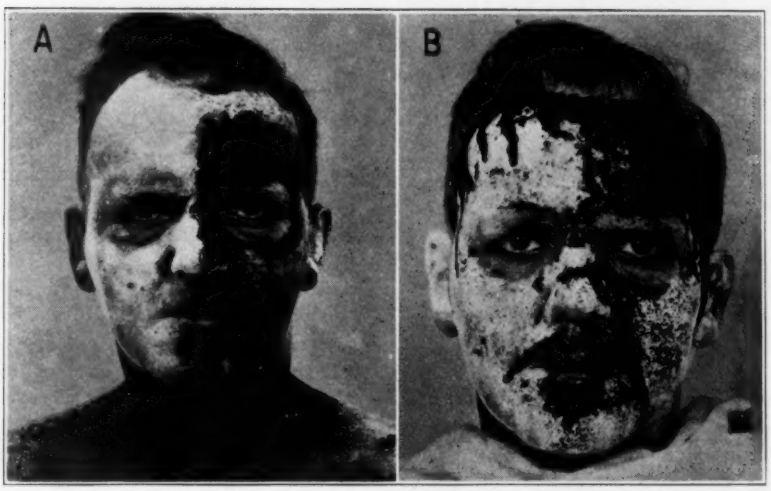

Fig. 3.—Resection of the right superior cervical sympathetic ganglion. *A*, heat sweating; *B*, pilocarpine sweating, one year after sympathectomy.

of the supraorbital and facial nerves failed to abolish the sweating produced by pilocarpine and mecholyl.

4. *Sweating Responses Associated with Sympathectomy.*—The cases in which sympathectomy was done will be divided into two groups: I. Resection of postganglionic fibers, such as superior cervical and low thoracic ganglionectomy. II. Combined resection of preganglionic and postganglionic fibers, such as cervicothoracic and lumbar ganglionectomy.

I. Section of Postganglionic Sympathetic Fibers:

Case 8.—In R. J. the right superior cervical ganglion had been removed a year before.

Experiment A (fig. 3*A*): A heat sweating test showed complete anhidrosis over the right side of the face.

Experiment B (fig. 3*B*): Pilocarpine produced sweating on both sides of the face; however, it was definitely diminished on the right.

CASE 9.—In L. B. the left superior cervical ganglion was removed for relief from angina pectoris.

Experiment A: A heat sweating test showed complete anhidrosis over the left side of the head.

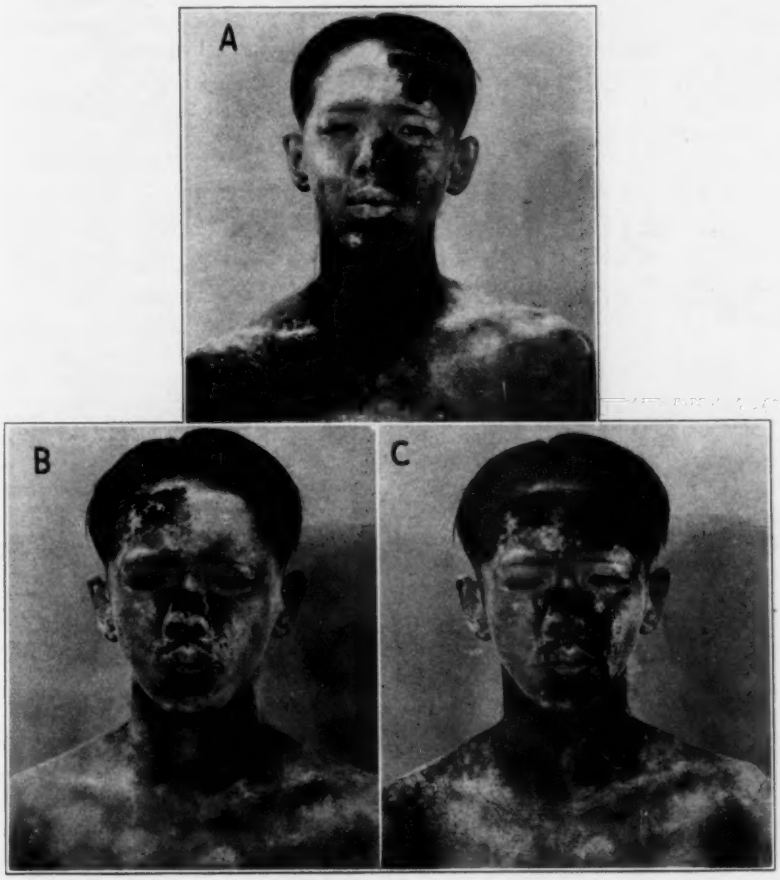

Fig. 4.—Lesion of the right superior cervical sympathetic ganglion. *A*, heat sweating; *B*, an early stage, and *C*, a late stage, of pilocarpine sweating.

Experiment B: The pilocarpine test, nine days after the operation, produced a mild increase in sweating over the left side of the forehead as compared with that over the normal right side. Sweating over the left cheek, however, was slightly diminished.

Experiment C: A mecholyl test done ten days after the operation produced a definite increase in sweating over the left side of the forehead. Sweating over other areas of the left side of the face was slightly less pronounced than were the corresponding parts of the right side.

Experiment D: The pilocarpine test was repeated more than three months after the operation. At this time there was only slight initial hyperhidrosis over the left side of the forehead. In the later stages of the test, however, there was considerable diminution of the sweating on the left side as compared with that on the normal right side.

CASE 10.—Paralysis of the right cervical portion of the sympathetic chain developed in H. C. K. after typhoid.

Experiment A (fig. 4 *A*): A heat sweating test showed complete anhidrosis over the right side of the face. There was "perilesionary" hyperhidrosis over the right side of the neck and the right shoulder.

Experiment B (fig. 4 *B* and *C*): The pilocarpine test at the beginning produced sweating over the right side of the face only, particularly the forehead

Fig. 5.—Bilateral resection of the tenth, eleventh and twelfth thoracic sympathetic ganglia. *A*, heat sweating; *B*, pilocarpine sweating, three weeks after operation.

(fig. 4 *B*). During the final stages of the test sweating over the right side lagged behind that over the normal left side (fig. 4 *C*).

CASE 11.—In F. M. the tenth, eleventh and twelfth thoracic ganglia were removed on both sides and the major and minor splanchnic nerves also were resected.

Experiment A (fig. 5 *A*): A heat sweating test three weeks after the operation revealed a wide band of anhidrosis over the ninth, tenth and eleventh dorsal dermatomes bilaterally.

Experiment B (fig. 5 *B*): The pilocarpine test also disclosed an area of complete anhidrosis bilaterally, which included the tenth and eleventh dorsal dermatomes.

CASE 12.—In E. P. two weeks previously, the tenth, eleventh and twelfth dorsal sympathetic ganglia were removed bilaterally, together with the major and minor splanchnic nerves.

Experiment A: The heat test revealed complete anhidrosis over the tenth, eleventh and twelfth dorsal dermatomes on both sides.

Experiment B: The combined action of general overheating, local application of heat over the abdominal area and injection of 12 mg. of mecholyl produced the same result as that in experiment A.

Experiment C: The combined action of general overheating, local application of heat over the abdomen and injection of 16 mg. of pilocarpine hydrochloride again produced the same result as that in experiment A.

II. Combined Section of Preganglionic and Postganglionic Fibers: Cervicothoracic sympathectomy severs the postganglionic fibers to the upper extremity and the preganglionic fibers to the head and neck. Lumbar sympathectomy interrupts the postganglionic fibers for the second, third and fourth lumbar nerves and the preganglionic supply for the fifth lumbar nerve and from the first to the fifth sacral nerves.

CASE 13.—A. S. had resection of the right inferior cervical and the first and second thoracic ganglia.

Experiment A (fig. 6*A*): The heat sweating test showed loss of sweating over the right side of the head, neck and upper part of the chest and the right upper extremity.

Experiment B (fig. 6*B*): Eight days after operation injection of pilocarpine produced marked increase of sweating over the right side of the face, particularly the forehead, and the right side of the neck. There was marked diminution of sweating, however, over the right shoulder, the upper part of the chest on the right and the upper part of the right arm. Almost no perspiration appeared over the right forearm and hand. The normal left upper extremity perspired profusely.

Experiment C (fig. 6*C*): Nine days after operation mecholyl had practically the same effect as pilocarpine.

CASE 14.—In H. W. the inferior cervical and first and second thoracic ganglia were removed bilaterally.

Experiment A (fig. 7*A*): The heat sweating test revealed anhidrosis over the head, neck, upper part of the chest and both arms.

Experiment B (fig. 7*B*): Two weeks after operation pilocarpine produced excessive perspiration over the head and neck. Moderate sweating occurred over the sympathectomized area of the upper part of the chest, but no sweating was seen below this area. The upper extremities showed little sweating.

Experiment C (fig. 7*C*): Two weeks after operation mecholyl produced excessive sweating over the face and neck. Perspiration over the upper part of the chest was normal, but an increase was noted at the lower border of the sympathectomized area (so-called perilesionary hyperhidrosis). Both upper extremities, the right more than the left, showed considerable perspiration, of irregular distribution.

CASE 15.—In W. H. the second, third and fourth sympathetic lumbar ganglia were resected on the left.

Experiment A: Ten days after operation the heat sweating test (on the anterior aspects of the legs only) revealed anhidrosis over the left lower extremity below the first lumbar dermatome.

Experiment B: Injection of pilocarpine eleven days after operation (the anterior aspects of the legs only being tested) produced moderate sweating of the

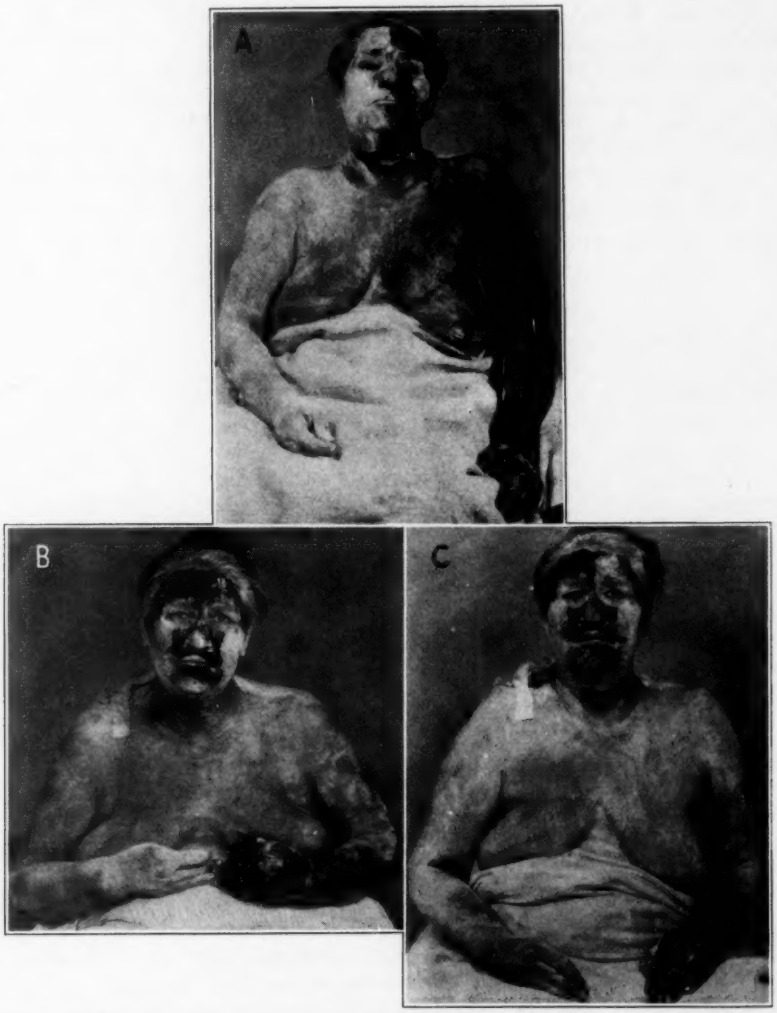

Fig. 6.—Resection of the right inferior cervical and the first and second thoracic sympathetic ganglia. *A*, heat sweating; *B*, pilocarpine sweating, eight days after sympathectomy, and *C*, mecholyl sweating, nine days after sympathectomy.

normal right leg and a zone of mild "perilesionary" hyperhidrosis over the first lumbar dermatome on the left. All other parts of the left leg remained dry.

Experiment C: Injection of mecholyl twelve days after operation (the anterior surfaces of the legs only being tested) produced only slight sweating over the

normal right leg. On the sympathectomized side dustlike traces of perspiration appeared as far down as the fourth lumbar dermatome, while the left foot remained dry.

Experiment D: The mecholyl test was repeated after three months, with similar results.

CASE 16.—H. S. the second, third and fourth lumbar sympathetic ganglia were removed bilaterally.

Experiment A (fig. 8): The heat sweating test (two weeks after operation, on the anterior and posterior surfaces of the legs) demonstrated anhidrosis of both lower extremities below the second lumbar dermatome. Mild sweating occurred in the second lumbar dermatome, and "perilesionary" hyperhidrosis, in the first lumbar dermatome.

Experiment B: Injection of pilocarpine (only the anterior surface was tested) showed the same results as those produced by the heat test.

Experiment C (fig. 9): Injection of mecholyl (the anterior and posterior surfaces were tested) produced an area of "perilesionary" hyperhidrosis marking

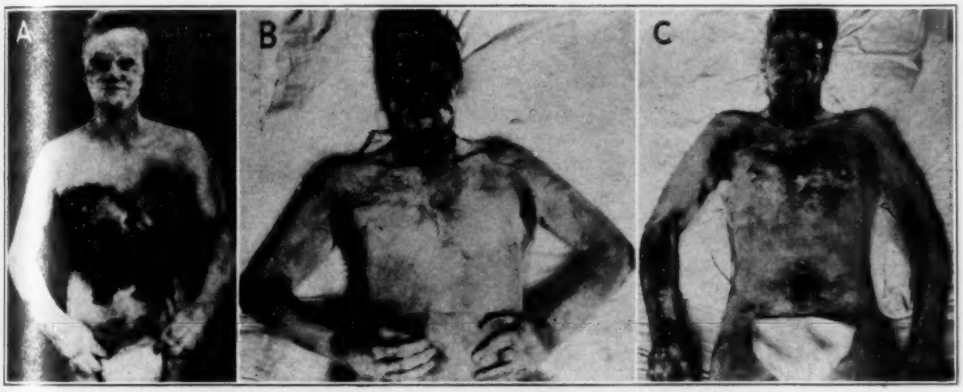

Fig. 7.—Bilateral resection of the inferior cervical and the first and second thoracic sympathetic ganglia. *A*, heat sweating; *B*, pilocarpine sweating, two weeks after sympathectomy, and *C*, mecholyl sweating, two weeks after sympathectomy.

the borderline between the first and the second lumbar dermatome. Slight sweating occurred in the second and third lumbar dermatomes, but none in the fourth and fifth lumbar and the first, second and third sacral dermatomes. Pronounced perspiration, however, appeared in the fourth and fifth sacral dermatomes.

The sweating response to pilocarpine and mecholyl following sympathectomy shows considerable variation. In general, section of postganglionic fibers leads to diminution in sweating produced by both pilocarpine and mecholyl. In certain persons there is a more pronounced response to mecholyl. Superior cervical ganglionectomy produces only moderate hypohidrosis, which apparently becomes more obvious with time. Some of the patients show hyperhidrosis during an early stage of the test, followed by hypohidrosis. After cervicothoracic sympathectomy pronounced diminution in sweating is noted in the upper

extremity. Low thoracic and lumbar sympathectomies lead to marked and frequently almost complete, loss of pilocarpine and mecholyl sweating. Conditions that usually produce maximum peripheral vasodilatation (prolonged application of general and local heat combined with mecholyl or pilocarpine) also fail to evoke or increase the perspiration.

Fig. 8.—Heat sweating after bilateral resection of the second, third and fourth lumbar sympathetic ganglia.

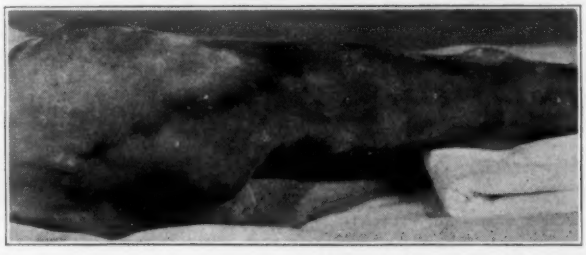

Fig. 9.—Mecholyl sweating, two weeks after sympathectomy, in the same case as that illustrated in figure 8.

Section of preganglionic fibers of the head and neck (cervicothoracic ganglionectomy) produces a strong or increased response to pilocarpine and mecholyl in the first weeks after the operation. In time, however, the intensity of the reaction lessens. Section of the preganglionic fibers of the sacral segments (lumbar ganglionectomy) leads to a diminished

response in the upper sacral dermatomes and a relatively stronger response in the lower sacral dermatomes.

5. *Sweating Responses Associated with Lesions of the Spinal Cord.*—I. Lesion of the Gray Matter, Involving Especially the Intermediolateral Columns.

CASE 17.—S. K., suffered from cervicordorsal syringomyelia, with more marked involvement of the right side.

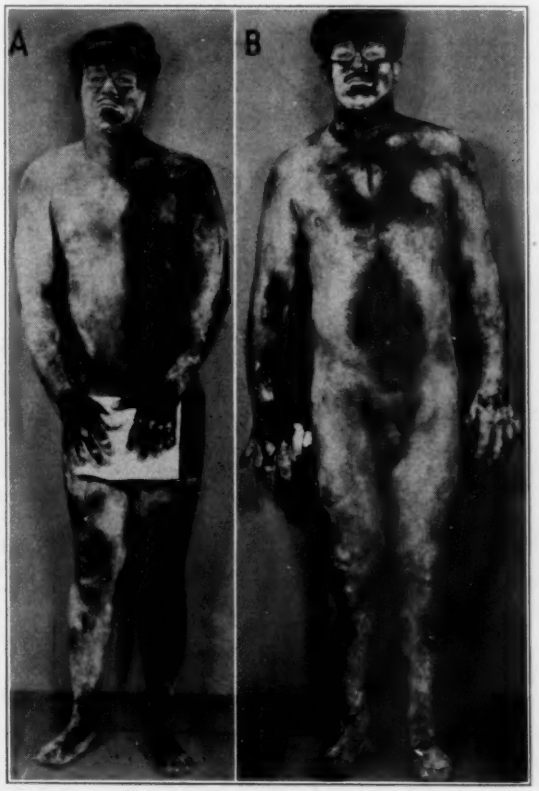

Fig. 10.—Cervicodorsal syringomyelia, predominantly on the right side. *A*, heat sweating; *B*, pilocarpine sweating.

Experiment A (fig. 10 *A*): The heat sweating test showed severe hypohidrosis over the entire right side, being pronounced over the right half of the head, neck and upper part of the trunk and the right upper extremity and less pronounced over the right leg.

Experiment B (fig. 10 *B*): Pilocarpine produced some hyperhidrosis over the right side of the face and right upper extremity. Sweating was equally distributed over the trunk and slightly diminished over the right leg.

II. Complete Transverse Lesion of the Spinal Cord.

CASE 18.—Seven years ago, I. J. suffered a fracture of the spine with complete destruction of the spinal cord at the level of the fifth dorsal segment. While total

motor and sensory paralysis has been present since the injury, some spinal automatisms have returned in time, e. g., defense reflexes, "automatic bladder" and erection.

Experiment A (fig. 11 *A*): The heat sweating test revealed that perspiration over the trunk diminished gradually from the third rib downward; both legs presented complete anhidrosis.

Experiment B (fig. 11 *B*): Pilocarpine evoked excessive sweating over the entire trunk and lower extremities except the feet, which remained dry.

Lesions of the vegetative pathways within the cord (e. g., destruction of the intermediolateral column) abolish thermoregulatory sweating, but tend to increase the pilocarpine response. Total transverse section of the spinal cord leads to loss of thermoregulatory sweating below the level of the lesion,[13] whereas pilocarpine sweating is well preserved or exaggerated. The increase in pilocarpine sweating may be greater with lesions of the spinal cord than with those of the preganglionic fibers outside the cord.

Fig. 11.—Transverse lesion of the spinal cord at the fifth thoracic segment. *A*, heat sweating, and *B*, pilocarpine sweating.

GENERAL COMMENT

1. *Problem of the Central Versus the Peripheral Action of Pilocarpine.*—There is little or no clinical or experimental evidence that pilocarpine when administered subcutaneously acts directly on a parasympathetic center in the diencephalon. The effect of pilocarpine in cases of lower thoracic and lumbar sympathectomy might suggest such a possibility, for the sweating response in these cases is similar to that following the application of heat. It is more likely, however, that the loss of pilocarpine sweating over the lower part of the body is explained on a basis other than the assumption of a central action of the drug (see page 287).

13. The level of thermoregulatory sweating may not be sharply defined and may not correspond to the sensory level.

The absence of pilocarpine sweating in the area where the circulation has been interrupted suggests that the drug reaches the periphery through the blood stream. The preservation of pilocarpine sweating after complete section of the spinal cord at the level of the fifth dorsal segment proves that the pilocarpine response does not originate from higher nerve centers, as all descending pathways are interrupted.

In one of the cases reported by Cushing,[1] intraventricular injection of 2.5 mg. of pilocarpine elicited generalized vasodilatation and sweating except in the area supplied by the divided supraorbital nerve. When pilocarpine is administered subcutaneously in cases of degenerative lesions of peripheral nerves the vasodilator effect persists, in spite of the abolition of sweating. The absence of both sweating and flushing in Cushing's case implies, therefore, a central origin of the phenomena of sweating and vasodilation, since a similar result is obtained by the heat method. It would be desirable to repeat Cushing's experiment with intraventricular injection of pilocarpine after one supraorbital nerve has been blocked with procaine hydrochloride. No sweating would occur in the anesthetic area if the response is of central origin, but perspiration in the area of the blocked nerve would not be materially changed if the action of the drug is peripheral. Another fact speaks for the central effect of intraventricular injection of pilocarpine, namely, that a dose as small as 2.5 mg. never produces generalized sweating and vasodilatation when administered subcutaneously; as a matter of fact, it leads to scarcely any reaction at all.

It is our impression, therefore, that the action of pilocarpine differs, depending on whether the drug is injected hypodermically or into the cerebral ventricles. Apparently, the intraventricular injection of a small dose produces a central response, whereas the subcutaneous injection acts peripherally. The sweating following intraventricular administration of pilocarpine may be of a nonspecific nature. This seems to be borne out by the similar effect produced by intraventricular injection of solution of an extract of posterior pituitary, although this drug is not parasympathomimetic. Furthermore, the experiments of Hasama [8] proved that various forms of local stimulation (thermic, electrical and chemical) of the hypothalamus may produce identical results.

2. *Action of Pilocarpine and Mecholyl on Nerve Endings and Sweat Glands.*—Having determined that pilocarpine administered subcutaneously acts peripherally, we shall now attempt to localize the effect of the drug more accurately.

Procaine block of a peripheral nerve interrupts the conductivity of all fibers temporarily, resulting in complete loss of sensation, loss of thermoregulatory sweating and vasomotor and somatic motor paralysis. The perspiration responses to pilocarpine and mecholyl, however, show

only slight diminution. Hence it must be assumed that in such a case the action of the drug takes place distal to the site of injection.

After surgical section of a peripheral nerve, however, the sweating response to pilocarpine and mecholyl is soon abolished. In a case of section of the supraorbital nerve complete loss of perspiration was found sixteen days after the injury. In another observation anhidrosis was demonstrated eight days after the lateral cutaneous nerve of the forearm was sectioned. Experimental section of peripheral nerves in animals and observations on injuries of nerves in man have shown that the secondary degeneration of the fibers to the finest nerve endings begins a few hours after the injury. Within two weeks the degeneration has advanced to the point at which the conduction of nerve impulses is completely interrupted; i. e., the end organs are denervated. The sweat glands themselves, however, do not degenerate within such a short period; in fact, they show no appreciable anatomic change, even after long-standing denervation. Since the completely denervated, but otherwise intact, sweat glands cannot be induced to secrete, the normal action of pilocarpine and mecholyl must depend on the presence of intact, functioning nerve endings.

In contrast to the observations in man, Langley and Anderson [3] showed that in the cat complete nerve degeneration is followed by marked diminution, but not abolition, of pilocarpine sweating. The possibility of a direct action of the drug on the sweat glands must, therefore, be admitted. Nevertheless, the observations in man do not necessarily contradict the results of the experiments on animals. They seem to indicate that a much larger quantity of the drug is required to excite the sweat glands themselves than to stimulate the corresponding nerve endings.

It has been stated that absence of pilocarpine sweating associated with lesions of peripheral nerves is due to circulatory changes. The marked arteriolar spasm and capillary stasis present with many lesions of this type were thought to prevent the pilocarpine from reaching either the endings of the sweat nerves or the sweat glands. This surmise is unlikely because the aforementioned vasomotor changes are rarely confined to the area supplied by the degenerated nerve, whereas the loss of sweating is practically identical with that area. Furthermore, pilocarpine still produces vasodilatation in the anhidrotic area. Consequently, the circulation must be sufficient to allow an adequate access of pilocarpine to the periphery.

3. *Fibers Acted On by Pilocarpine and Mecholyl.*—I. Role of the Sympathetic (Thoracolumbar) Fibers: In the introductory section, the term "cholinergic" was used for the designation of nerve fibers which are stimulated by parasympathomimetic drugs and convey nerve

impulses to their end organs by the intermediate action of a chemical transmitter (acetylcholine). In experiments on animals, Dale and Feldberg [10] found conclusive evidence that the thoracolumbar system carries cholinergic fibers. They stimulated by faradic current the peripheral end of the sectioned lumbar portion of the chain in cats. Simultaneously with the outbreak of sweating, a substance with acetylcholine-like properties appeared in the perfusion fluid of the feet. The clinical observations in man support the view of Dale and Feldberg that some of the postganglionic sympathetic fibers are of cholinergic nature and that therefore degeneration of postganglionic fibers must entail diminution of the response to pilocarpine or mecholyl. The moderate hypohidrosis after cervicocephalic postganglionic deefferentation is in contrast to the severe hypohidrosis (or almost complete anhidrosis) following low thoracic or lumbar deefferentation. These regional differences are best explained by the assumption that the cervical portion of the sympathetic chain contains only a few, while the lower thoracic and lumbar portions contain most, of the cholinergic fibers for the sweat glands. One must not overlook the fact, however, that normally the response to pilocarpine and mecholyl is much greater over the upper than the lower part of the body. Preservation, or exaggeration, of the response to pilocarpine and mecholyl after preganglionic deefferentation may suggest an inhibitory influence of the preganglionic on the peripheral sympathetic neuron comparable with the inhibitory effect of the upper motor neuron on the lower. Exaggeration of the response is more apparent when the supraspinal sympathetic neuron is affected.

Modifications of pilocarpine sweating following sympathectomy have been explained: (*a*) by a change in the circulation of the blood; or (*b*) by sensitization of the deefferentated sweat glands.

(*a*) It was thought that vasoconstrictor paralysis caused an increase in pilocarpine sweating because a larger amount of the drug reached the skin through a widened vascular bed. Such an assumption can be easily refuted by the facts observed. Areas of postganglionic denervation of the extremities and trunk show a decreased response to pilocarpine and mecholyl in spite of an increased blood flow (recognized by the elevation of the cutaneous temperature).

(*b*) It is known that after sympathectomy the deefferentated end organs, such as smooth muscle fibers or gland cells, become hypersensitive to direct chemical stimulation (White [14]). Substances with a possible direct effect on sweat glands may either be introduced in the course of an experiment (e. g., pilocarpine and mecholyl) or be produced by the physiologic activities of the body (e. g., epinephrine and acetylcholine).

14. White, J. C.: The Autonomic Nervous system, New York, The Macmillan Company, 1935.

It is unlikely that sensitization of the sweat glands to the injection of drugs explains sufficiently the sweating reactions after sympathectomy. Were this the case, one would expect an increase in sweating induced by pilocarpine or mecholyl; actually, however, definite hypohidrosis is observed over the areas of postganglionic denervation (except the face and neck). It appears equally improbable that the diminished sweating response following section of postganglionic fibers is due to sensitization to epinephrine. The inhibitory influence of epinephrine on sweating probably depends on its vasoconstrictor effect rather than on a direct inhibitory action on the sweat glands. In an observation on low thoracic sympathectomy and section of the splanchnic nerves (case 12) pilocarpine and mecholyl failed to evoke perspiration, although the application of intense local heat should have counteracted the possible vasoconstrictor effect of epinephrine and provided for maximal vasodilatation in the sympathectomized skin. Furthermore, the level of epinephrine in the blood was supposedly low in this instance, since the adrenal glands had been denervated by section of the splanchnic nerves.

There is, however, evidence for sensitization of the deefferentated sweat glands to acetylcholine. This will be discussed later.

II. Role of the Parasympathetic Fibers: Interruption of postganglionic sympathetic fibers for the head (superior cervical ganglionectomy) reduces pilocarpine sweating, but only complete denervation (section of the peripheral branches of the fifth nerve) abolishes it completely. The fifth cranial nerve, therefore, must contain many cholinergic fibers which do not arise in the sympathetic chain. In fact, cholinergic fibers pass through various cranial parasympathetic nerves (fifth, seventh, ninth and tenth) performing secretory or vasodilator functions. The richness of the cranial cholinergic supply may account for the intensity of the physiologic reaction to pilocarpine and mecholyl over the head. On the other hand, the scanty sweating induced by drugs after postganglionic denervation of the extremities and trunk suggests the presence of only a few nonsympathetic cholinergic fibers in the spinal nerves. The cholinergic fibers considered here are the spinal vasodilator fibers, the anatomic characteristics of which have not been definitely established; probably they are identical with the efferent fibers in the posterior roots.

Furthermore, an observation by Guttmann [7b] and recent experiments of Kuré and his collaborators [15] suggest the presence of direct parasympathetic sweat fibers in the anterior roots.

According to present anatomic knowledge, the sweat glands possess a postganglionic sympathetic, but no direct parasympathetic, innervation.

15. Kuré, K.; Okinaka, S.; Maéda, S., and Kato, H.: Studien über Schweissdrüseninnervation, Arch. f. d. ges. Physiol. **237**:40-53, 1936.

The difficulty which this morphologic fact has created for the interpretation of physiologic experiences seems to have been overcome by the work of Dale and his collaborators. Since the vasodilator fibers are representative of the parasympathetic (cholinergic) cutaneous innervation, the mode of their function must be analyzed in detail. When cutaneous vasodilator fibers are excited by a physiologic (neurodynamic) stimulus, the capillaries and smaller blood vessels widen under the influence of locally liberated acetylcholine, which is soon destroyed by an enzyme (esterase) in the blood.

The effect of a subcutaneous injection of pilocarpine or mecholyl is different and may be described as follows: The drug reaches the skin via the blood stream. It must act directly on the smooth muscle fibers of the smaller blood vessels and on the capillaries, producing vasodilatation, because this effect is observed even after complete degeneration of the peripheral nerves. Customary doses of the drugs produce no visible direct effect on the sweat glands, as proved by the presence of anhidrosis in cases of complete denervation. Another, and more important, effect of pilocarpine or mecholyl consists in powerful stimulation of cholinergic nerve endings, releasing locally large quantities of acetylcholine, which may leak into the neighboring tissues and obtain access to the adjacent sweat glands. Thus, not only vasodilatation but perspiration occurs. Assuming, then, that the pilocarpine or mecholyl diffusing from the blood vessels is unable to excite the sweat glands directly, owing to its infinitesimal concentration, the effect of the drug is amplified by the neurochemical "starter" or relay system of the vasodilator nerves. This theory explains how the stimulation of cutaneous vasodilator fibers by pilocarpine produces sweating indirectly by chemical transmission.

In a case of degeneration of peripheral nerves, then, pilocarpine fails to elicit sweating because the relay mechanism of the vasodilator is destroyed. If only the postganglionic sympathetic fibers have degenerated, the remaining parasympathetic cholinergic fibers (vasodilator nerves) continue to liberate acetylcholine, and thus maintain visible perspiration. The abundance of the cranial parasympathetic nerve supply accounts in part for the strong response to pilocarpine and mecholyl after superior cervical ganglionectomy. On the other hand, the scarcity of the nonsympathetic cholinergic fibers in all other areas of the body explains the more or less severe hypohidrosis following section of the postganglionic fibers supplying the trunk and the extremities.

The abundant supply of cranial parasympathetic cholinergic nerves accounts not only for the preservation of pilocarpine sweating after superior cervical ganglionectomy but for the phenomenon which must be interpreted as sensitization to acetylcholine of the deefferentated sweat glands of the face. Thus, in case 10 earlier and more pro-

nounced sweating appeared on the side of the sympathetic paralysis, indicating hypersensitiveness of the deefferentated sweat glands as compared with the response of the normal glands. Later in the test the side of the sympathetic paralysis exhibited mild hypohidrosis, presumably due to loss of sympathetic cholinergic fibers. The hypersensitiveness of the sweat glands seems to be greatest in cases in which the degeneration of postganglionic fibers is of short duration; in time the direct response of the glands gradually diminishes, until it may reach a subnormal level. This explains the early strong sweating response after cervical sympathectomy as compared with the markedly diminished reaction after long-standing deefferentation (cases 8 and 9).

SUMMARY

Sweating responses following subcutaneous injection of pilocarpine and mecholyl were studied in man under physiologic and pathologic conditions. The influence of obstruction of the circulation and of various lesions of the nervous system was investigated. When injected subcutaneously, pilocarpine and mecholyl act on the periphery through the circulating blood. They have apparently no effect on the central nervous system. Pilocarpine and mecholyl stimulate the endings of cholinergic nerve fibers. Administered subcutaneously in customary doses, both drugs usually show no visible direct action on the sweat glands.

There is evidence that two sets of cholinergic fibers exist: (1) postganglionic sympathetic and (2) parasympathetic cholinergic fibers. The majority of the cholinergic fibers for the trunk and extremities seem to pass through the thoracolumbar sympathetic system. The cholinergic fibers supplying the head, however, travel largely via cranial parasympathetic nerves.

Cholinergic fibers convey nerve impulses indirectly to their end organs by releasing a substance with the properties of acetylcholine. This chemical transmitter may produce an effect on sweat glands, even though the cholinergic fibers (at least those of parasympathetic origin) make no direct anatomic contact with the sweat glands.

Sweat glands deprived of their postganglionic sympathetic innervation tend to become hypersensitive to direct chemical stimulation; in particular, the deefferentated sweat glands of the face may show sensitization to acetylcholine liberated by the remaining parasympathetic cholinergic fibers.

INTRACEREBRAL BLOOD FLOW

AN EXPERIMENTAL STUDY

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During the past ten years, Forbes and his co-workers have published the results of their experiments on the activity of the cerebral circulation. This work has been confined for the most part to the pial vessels, of which they have worked out in detail the reactions to many agents. More recently, Schmidt and Pierson [1] have studied the activity of the blood flow in the substance of the brain in various areas by means of a thermoelectric method similar to that reported by Gibbs.[2] These studies have thrown a great deal of light on the much disputed subject of the cerebral circulation and have established certain well defined facts concerning its activity. In the hope of adding data in this field, the thermoelectric method of Gibbs was used to study the effect of various agents on the blood flow through the parietal area of the cat's brain.

TECHNIC

The device for recording the blood flow consists, in brief, of two couples of constantan and copper connected in series to a potentiometer and a galvanometer.[3] One of the couples has, incorporated in its tip, a small piece of resistance wire that can be brought to any temperature desired by passing through it a fixed current. This heated, or "hot," junction is thrust into the area of the brain to be studied to a depth of from 4 to 10 mm. The other, or "cold," junction is placed in a similar position in the other hemisphere. As the junctions are so connected that the current set up in one is opposed by that set up in the other, changes in the temperature of the animal are canceled, and only the current set up by the

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The material in this paper was presented in the form of a thesis to the McGill University Faculty of Medicine in May 1936, in partial fulfilment of the requirements for the degree of Master of Science.

1. (*a*) Schmidt, C. F., and Pierson, J. C.: The Intrinsic Regulation of the Blood Vessels of the Medulla Oblongata, Am. J. Physiol. **108**:241 (April) 1934. (*b*) Schmidt, C. F.: The Intrinsic Regulation of the Circulation in the Hypothalamus of the Cat, ibid. **110**:137 (Nov.) 1934; The Intrinsic Regulation of the Circulation in the Parietal Cortex of the Cat, ibid. **114**:572 (Feb.) 1936.

2. Gibbs, F. A.: A Thermoelectric Blood Flow Recorder in the Form of a Needle, Proc. Soc. Exper. Biol. & Med. **31**:141 (Oct.) 1933.

3. The blood flow recorder was made by Mr. A. J. Lush, of the Rawson Instrument Co., Cambridge, Mass., from plans made by Dr. F. A. Gibbs.

heating of the "hot" junction is recorded. This current will fluctuate, owing to the cooling effect of the blood flow through the surrounding brain tissue. The "hot" junction is about 1.5 mm. in diameter, and the "cold" junction, 1 mm. The heat used in the "hot" junction is of the order of from 1.5 to 2 C. and has been found, by histologic study of the microglial reaction, to cause little damage to the brain immediately surrounding it. After the potentiometer has been standardized, the beam from the galvanometer mirror is thrown onto a scale with a movable pointer. This pointer is attached by a cord to a writing arm on the kymograph. The sensitivity of the apparatus is then tested by compressing the neck of the animal for a short time; the result of this is shown in *L* in the accompanying figure.

Cats were used in all the experiments. They were anesthetized by the intraperitoneal injection of dial, the dose varying from 0.3 to 0.6 cc. per kilogram of body weight. An attempt was made to keep the anesthesia as light as possible, as the animals were more reactive and the results more consistent.

Two burr holes were placed over the highest points of the parietal bones, and the dura and arachnoid beneath them were incised. Through these incisions the thermocouples were thrust into the cortex of the parietal lobes, to the desired depth. A cisternal puncture was then made and enough fluid removed so that plaster of paris, placed in the burr holes around the thermocouples, could dry. This substance formed a water-tight seal and, at the same time, held the couples firmly in place. The fluid that had been removed was replaced and the cisternal needle connected with a manometer. This manometer was fitted with a movable indicator connected by a cord to a recording arm on the kymograph. The blood pressure was recorded from a cannula in the femoral artery, and the respiratory rate, by a toy balloon tied around the chest and connected to a recording tambour. A thyratron stimulator was used for all nerve stimulations.

The experimental criteria that were established by Forbes and his co-workers [4] were used as a guide and applied to the greatest possible extent. In brief, the following factors were found to be most important: The animal should be under light anesthesia; it should have a temperature not far from normal, and it should not be shivering or have hyperpnea.

A series of experiments were carried out as a control in order to determine the effect of body temperature on the apparatus. When the "hot" junction was not heated, general changes in the blood flow and body temperature did not displace the galvanometer beam significantly. Stimulation of the cervical portion of the sympathetic chain on one side likewise produced no significant change.

EXPERIMENTAL RESULTS

A. Action of the Vagus Nerve.—If artificial respiration was given, central stimulation of the vagus nerve caused a decrease in the blood flow which paralleled the fall in the systemic blood pressure. There was usually a slight increase in the cerebrospinal fluid pressure. *A* in the figure shows a typical response.

B. Action of the Cervical Portion of the Sympathetic Chain.—Peripheral stimulation of the cervical portion of the sympathetic trunk

4. Forbes, H. S.: The Cerebral Circulation: I. Observation and Measurement of Pial Vessels, Arch. Neurol. & Psychiat. **19**:751 (May) 1928.

was found in the majority of experiments to cause a decrease in the blood flow through the ipsilateral cortex. This reaction failed to appear if experimental conditions, as already noted, were not satisfactory. A slight decrease in the blood flow through the contralateral parietal cortex was obtained on a few occasions, but the majority of the experiments showed no significant change. In the ipsilateral cortex, as the blood flow decreased there was little, if any, change in the blood pressure or pulse. In the greater number of experiments there was a slight decrease in the cerebrospinal fluid pressure. The decrease in the blood flow started after a lag of from two to twenty seconds, and the rate of flow continued to decrease for from ten to sixty seconds after stimulation had ceased. It then slowly returned to the initial level, attaining it sometimes in a minute or two and at other times not for several hours. The reaction could occasionally be repeated. Artificial respiration had no measurable effect on the response. In the figure, *B* shows a typical reaction. No definite correlation was found between the strength of the current and the change in the blood flow; at times there was a marked decrease with a current scarcely strong enough to produce miosis, while at other times a much stronger current gave only a slight reaction.

C. Action of Carbon Dioxide.—Inhalation of carbon dioxide caused a tremendous increase in the blood flow, and this increase seemed to be roughly proportional to the percentage of the gas in the mixture inhaled. The blood pressure was slightly increased in most experiments; the cerebrospinal fluid pressure was moderately increased in all experiments, and this increase was greater with gas mixtures having a high percentage of carbon dioxide. In the figure, *C* shows the reactions to mixtures containing 3 and 5 per cent of carbon dioxide, respectively. Rebreathing into a rubber bag gave substantially the same result, as is seen in the figure, *E*.

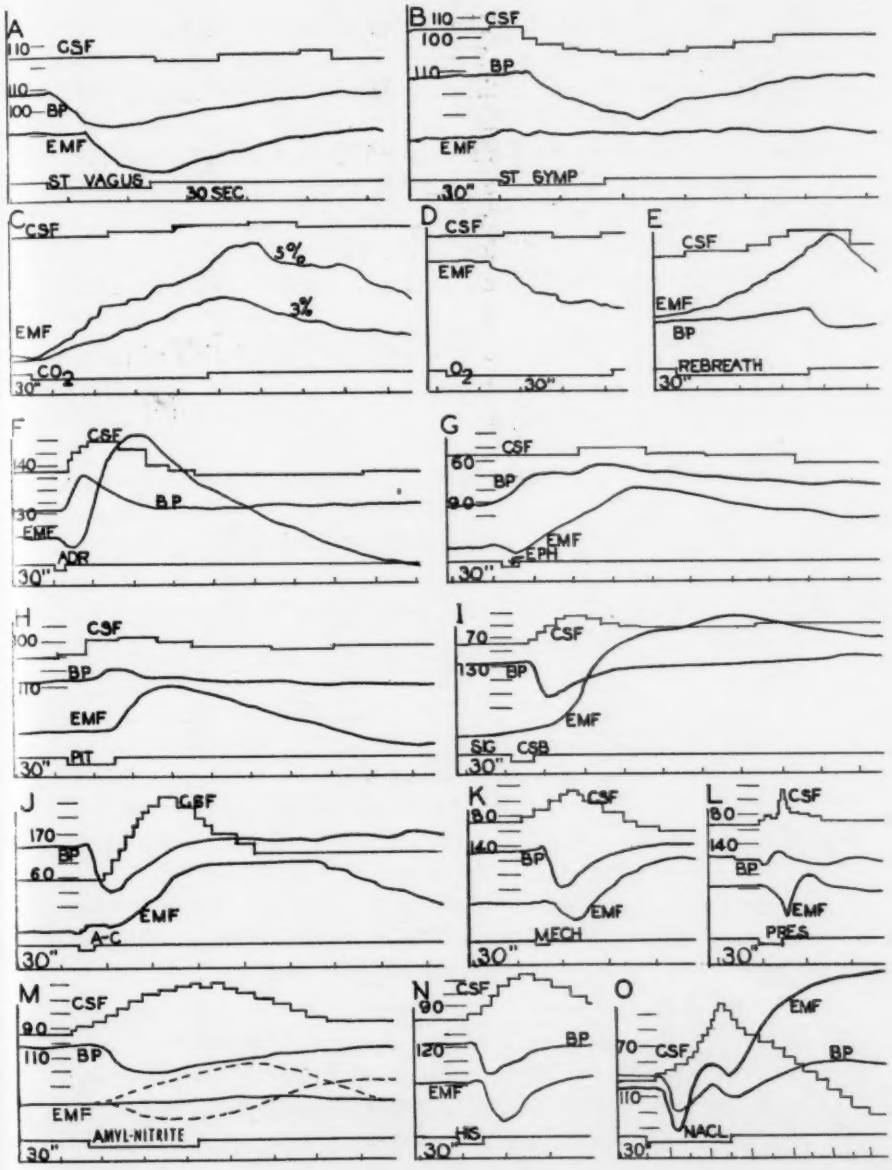
D. Action of Oxygen.—Inhalation of pure oxygen caused the blood flow to decrease slowly and to remain at a lowered level as long as the gas was administered. As is seen in the figure, *D*, the effect was in no way comparable to that obtained with carbon dioxide and was at times so slight as to fall almost within the bounds of experimental error. If atmospheric air was used and the rate of the respiratory exchange was increased, an effect similar to that obtained with pure oxygen was produced.

E. Action of Epinephrine.—The intravenous or intracarotid injection of epinephrine caused a rapid and marked increase in the blood flow, which was closely paralleled by similar changes in the systemic blood pressure and the cerebrospinal fluid pressure. The return of all three to the levels prior to injection was prompt, as is seen in the figure, *F*. It was occasionally noted that the blood flow did not fall

Explanation of Plate

All the experiments were performed with the use of artificial respiration. Dial anesthesia was used. The graduations for the blood pressure and the cerebrospinal fluid pressure all represent 1 cm. The expected experimental error does not exceed 10 mm. The lowest line on each chart gives intervals of thirty seconds, and the next line above represents the signal magnet. *CSF* stands for the cerebrospinal fluid pressure; *BP*, the blood pressure, and *EMF* the blood flow.

A, effect of stimulating the right vagus nerve centrally after section. The "hot" junction of the thermocouples was in the right parietal area. *B*, effect of stimulating the cervical portion of the sympathetic chain on the right side peripherally. The "hot" junction was in the right parietal area. *C*, effects of inhalation of mixtures containing 3 and 5 per cent, respectively, of carbon dioxide; *D*, effect of breathing pure oxygen; *E*, effect of rebreathing into a rubber bag; *F*, effect of the intracarotid injection of 1 cc. of a 1:100,000 solution of epinephrine hydrochloride; *G*, effect of intravenous injection of 0.5 cc. of a 1:200 solution of ephedrine sulfate; *H*, effect of intravenous injection of 1 cc. of a 1:25 dilution of solution of posterior pituitary U. S. P.; *I*, effect of intravenous injection of 125 mg. of caffeine with sodium benzoate U. S. P. in 2 cc. of physiologic solution of sodium chloride; *J*, effect of intravenous injection of 0.0025 mg. of acetylcholine chloride, freshly prepared in distilled water; *K*, effect of intravenous injection of 0.01 mg. of acetylbetamethylcholine chloride, freshly prepared in distilled water; *L*, effect of compression of the animal's neck, as a control for sensitivity of the blood flow recorder at the beginning and as shown in the end of each experiment; *M*, effect of inhalation of amyl nitrite, 3 trials on different animals, the changes in blood pressure and cerebrospinal fluid pressure having been about the same in the original records; *N*, effect of intravenous injection of 0.25 cc. of a 1:100,000 solution of histamine phosphate, freshly prepared in distilled water, and *O*, effect of intravenous injection of 20 cc. of a 10 per cent solution of sodium chloride.


A
110 CSF
110
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100
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CO2
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D
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O2
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30"
O
EMF
70 CSF
BP
110
NACL
30"

PLATE

again as rapidly as would have been expected. This was seen in animals that were under very deep anesthesia, or were otherwise in poor condition.

F. Action of Ephedrine.—The action of ephedrine was much the same as that of epinephrine. The extent and duration of the effect differed in that the increase in the records for the three factors was not as great, and the return to the initial level was much slower. The cerebrospinal fluid pressure was influenced least of all, and the increase was sometimes of a magnitude that fell within the expected experimental error. As was the case with epinephrine, there were occasional lags in the return of the blood flow to the level prior to injection. These occurred under experimental conditions of the same type. In the figure, *G* shows the typical response.

G. Action of Solution of Posterior Pituitary.—Solution of posterior pituitary given intravenously increased the blood flow, the blood pressure and the cerebrospinal fluid pressure. The rise and the fall in all three were roughly parallel, and the duration of the reaction was about midway between that to epinephrine and that to ephedrine. The reaction to a moderate dose is shown in the figure, *H*. If a large dose was given to an animal in poor condition, there was a lag in the return of the blood flow to the level before injection similar to that seen when epinephrine or ephedrine was given under similar circumstances.

H. Action of Caffeine.—Under light dial anesthesia, the effect of injection of moderate doses of caffeine with sodium benzoate U. S. P. was to increase the cerebral blood flow, decrease the blood pressure and increase the cerebrospinal fluid pressure slightly. The blood pressure returned to its initial level in the course of a few minutes, while the blood flow remained elevated for from ten minutes to two hours, depending on the dose and the condition of the animal. The cerebrospinal fluid pressure remained increased for about the same length of time as did the blood flow. In the figure, *I* shows the early part of a typical response. Larger doses tended to give a greater effect, while an increase in the depth of anesthesia lessened the effect.

I. Action of Acetylcholine.—Small doses of a freshly prepared solution of acetylcholine caused a great increase in the blood flow, as well as in the cerebrospinal fluid pressure, and a marked fall in the systemic blood pressure. In cases in which the blood pressure fell abruptly there was usually an initial transitory decrease in the blood flow. The reaction to the drug was short lived and was completely abolished by atropine. In the figure, *J* shows the usual response.

J. Action of Acetylbetamethylcholine.—The action of a freshly prepared solution of acetylbetamethylcholine differed from that of acetylcholine in that the increase in the blood flow and in the cerebrospinal

fluid pressure were not as great, while the change in blood pressure was about the same. The record of the blood flow nearly always showed an initial transitory decrease, which was most marked when the blood pressure fell abruptly. In general, the effect was more lasting than that caused by acetylcholine. In the figure, *L* shows the beginning of a typical response.

K. Action of Amyl Nitrite.—After inhalation of amyl nitrite there were a prompt drop in the blood pressure and an increase in the cerebrospinal fluid pressure. The blood flow varied somewhat in different experiments, as is seen in the figure, *M*, in which the records of the blood flow in three experiments are superimposed, the changes in the blood pressure and those in the cerebrospinal fluid pressure having been approximately the same. If the inhalation was continued for more than a minute or a minute and a half, the blood flow decreased as the blood pressure became greatly depressed. After the inhalation was stopped, the return of all three records to the preinjection level was prompt in all experiments.

L. Action of Histamine.—Solutions of histamine injected intravenously caused a decrease in the blood flow that was nearly parallel to the drop in the blood pressure. The cerebrospinal fluid pressure was greatly increased. In the figure, *N* shows the reaction obtained when artificial respiration was used. If it was not used there was, after the initial decrease in the blood flow, an increase that continued for some time after the blood pressure had returned to the preinjection level.

M. Action of Hypertonic Solutions.—After the use of hypertonic solutions of dextrose the reactions were so uncertain and contradictory that no attempt was made to evaluate them. Hypertonic solutions of sodium chloride, however, uniformly caused an increase in the blood flow, usually preceded by an initial drop. There was a slight decrease in the blood pressure, probably due to sodium poisoning, that lasted for about ten minutes. The cerebrospinal fluid pressure first increased rapidly and then decreased throughout the duration of the experiment, as is shown in *O* in the figure.

COMMENT

The present work was all done on the parietal area, and it must be remembered that the findings are applicable only to this region. Schmidt [1b] showed that the reaction to the same stimulus is not necessarily the same in different parts of the brain. It must also be noted that these experiments were done under dial anesthesia and that curare was not used to immobilize the animals.

The vagus nerve was found to be without active effect, the changes that were recorded being directly attributable to the depressed blood

pressure. This observation is in harmony with the reports by Pool, Forbes and Nason;[5] Schmidt and Pierson,[1a] and Schmidt.[1b] Schmidt reported that the vagus nerve had no effect on the hypothalamus and the parietal area.

The effect of stimulation of the cervical portion of the sympathetic chain caused a moderate decrease in the blood flow through the ipsilateral area. This finding is an agreement with the views recently expressed by Pool, Forbes and Nason and Schmidt, who showed that whereas the effect of sympathetic stimulation is slight and inconstant in the medulla, it is constant in the hypothalamic area and in the parietal region, being even more pronounced in the latter. Schmidt has demonstrated further that the effect of sympathetic stimulation is chiefly ipsilateral in the hypothalamus, while in the parietal area there is in addition a definite contralateral effect. This last finding has not been wholly borne out in the present work.

The marked effect of carbon dioxide has been emphasized by all recent investigators, and it is generally conceded that this effect is of primary importance. The increase in blood flow is of a magnitude which so far outstrips anything produced by nerve stimulation that Schmidt and Pierson and Wolff and Lennox[6] postulated that the chemical constitution of the blood is a far more important factor in the regulation of cerebral blood flow than is vasomotor control. The effect of inhalation of pure oxygen or of hyperventilation with air has a definite effect, which, however, is not comparable in magnitude to that of carbon dioxide.

The actions of epinephrine, ephedrine and solution of posterior pituitary have much in common; they all act on the cerebral circulation secondarily to their effect on the systemic blood pressure. No evidence of any direct effect on the cerebral blood flow in the parietal area has been found. With animals in poor condition they all exert what is probably a toning-up effect on the general circulation.

Caffeine, acetylcholine and acetylbetamethylcholine all cause an increase in the blood flow, in the face of depressed blood pressure; amyl nitrite in moderate amounts maintains the rate of the blood flow with a decrease in blood pressure, while histamine causes a decrease in blood flow that follows that of the blood pressure. Wolff[7] and Forbes, Wolff

5. Pool, J. L.; Forbes, H. S., and Nason, G. I.: The Effect of Stimulation of the Sympathetic Nerve on the Pial Vessels in the Isolated Head, Arch. Neurol. & Psychiat. **32**:915 (Nov.) 1934.

6. Wolff, H. G., and Lennox, W. G.: The Cerebral Circulation: XII. The Effect on Pial Vessels of Variations in Oxygen and Carbon Dioxide Content of Blood, Arch. Neurol. & Psychiat. **23**:1097 (June) 1930.

7. Wolff, H. G.: The Cerebral Circulation: XI. Action of Acetylcholine, Arch. Neurol. & Psychiat. **22**:686 (Oct.) 1929.

and Cobb [8] showed that these drugs all cause dilatation of the pial vessels. May it not be that a difference in the site of the dilatation in these cases accounts for the difference in the response?

The present findings are compatible with results recently obtained by Schmidt [1] in his study of the same area with a slightly different technic. The conclusion by Schmidt and Pierson [1a] that the blood vessels of the brain are in a state of intrinsically high tone and that their activity "depends on a variable dilatation rather than constriction" is borne out by the present findings.

CONCLUSIONS

In the parietal area of the cat's brain, with the animal under dial anesthesia the following observations were made.

1. The vagus nerve has no direct effect on the blood flow through either side of the brain.

2. Stimulation of the cervical portion of the sympathetic chain causes a decrease in the blood flow on the ipsilateral side.

3. Carbon dioxide is a powerful agent in increasing the blood flow.

4. Inhalation of pure oxygen or hyperventilation with atmospheric air causes a decrease in the blood flow.

5. Epinephrine, ephedrine and solution of posterior pituitary increase the blood flow secondarily to the increase in blood pressure.

6. Caffeine, acetylcholine and acetylbetamethylcholine cause an increase in the blood flow, in spite of depressed blood pressure.

7. Amyl nitrite in moderate amounts maintains the rate of blood flow in spite of depressed blood pressure.

8. Histamine decreases the blood flow secondarily to the decrease in blood pressure.

9. Hypertonic solutions of sodium chloride cause an increase in the blood flow.

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8. Forbes, H. S.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: X. Action of Histamine, Am. J. Physiol. **89**:266 (July) 1929.

MECHANISM OF AFTER-CONTRACTION

FURTHER STUDIES

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The phenomenon of after-contraction, though of considerable neurologic interest, has received comparatively little attention. It is regarded as the result of an after-discharge from the nervous system and may be elicited when any set of muscles, for instance, those involved in raising the extended arm or leg, is voluntarily kept in action against resistance for a period of time. The phenomenon consists of an involuntary repetition of the originally intended movement and a feeling of lightness or floating upward of the part following relaxation of the contracting muscles and removal of the resistance. Thus, if one stands against a wall and forcefully pushes the hand of the stiffly extended arm against it, then relaxes the contracting muscle group and steps away, the arm slowly rises toward a horizontal position. The subject who is performing this experiment for the first time, in complete ignorance of the expected result, is usually surprised at this involuntary contraction of his muscles and, if the eyes are shut, frequently expresses the opinion that his limb is being forced up by the experimenter.

The after-contraction, variously termed *phénomène d'automatisme, Kohnstammsche Phänomen* and *Nachbewegung,* has previously been studied by Salmon, Kohnstamm and others. It seems to us that the explanations of its mechanism thus far offered are not satisfactory. We have therefore reinvestigated the phenomenon in the hope that it may be explained in the light of more recent studies on the physiologic behavior of the nervous system.

METHOD

As the method employed in the study of the reaction has been described elsewhere,[1] only a brief description will be given here. Any muscle group in the

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1. Sapirstein, M. R.; Herman, R. C., and Wallace, G. B.: Am. J. Physiol. **119**:549, 1937.

body may be employed, but it was found convenient to record the flexion at the hip joint, with the knee extended. The subject stands on a platform, so that the supporting leg is high and the other hanging, as it were, to allow freedom of movement. A given weight connected by a cable which passes over a pulley is attached to one heel. At a given signal the subject is asked to raise the extended leg, when the leg is rotated forward through a small arc and the weight is lifted. When he is commanded to relax, the leg falls back to the normal hanging position. The weight is then detached, and the subsequent involuntary flexion is recorded. This is accomplished by means of a cord, attached to the heel, which passes over several directive pulleys and is connected with a lever which records the movement on a kymograph. The apparatus employed is essentially simple, and the principle is no different from that used with the arm pressed against the wall, except that a known force can be employed and the movements recorded. Permanent records are thus obtained, and significant changes can be measured (fig. 1, *1*).

PREVIOUS INVESTIGATION

In the experimental approach to the problem we have utilized the methods which are generally employed in the study of the human nervous system, namely, the pharmacologic, the physiologic and the clinical.

It has been demonstrated in pharmacologic investigations [2] that the after-contraction is markedly reduced after the ingestion of sodium bromide in relatively small doses of 2 Gm. In most cases the reaction is completely abolished by this dose, despite the fact that the knee jerk persists and there is little or no mental depression. On the other hand, caffeine in doses equivalent to that found in a cup of coffee (0.15 Gm.) stimulates the after-contraction. This effect is especially marked after previous depression by bromides. Other drugs (chloral hydrate, strychnine and barbital) were found to have lesser effects.

Physiologic studies [1] have also been illuminating. The after-contraction is sensitive to an increase in the force as well as the duration of the initial stimulus, i. e., the period of elevation of the extremity. Thus, when the initial stimulus is kept constant and the supported weight increased, the after-contraction also increases (fig. 1, *3*) until it reaches a maximum corresponding to the heaviest weight that can be lifted. On the other hand, with the load kept fixed the after-contraction increases with increase in the duration of the stimulus (fig. 1, *2*). Facilitation and reenforcement are readily illustrated with this phenomenon. Facilitation can be demonstrated by repeating the cycle of after-contraction at short intervals. When this is done the amplitude of the after-contraction progressively increases until the factor of fatigue enters, at which time the amplitude decreases (fig. 1, *4*).

2. Sapirstein, M. R.; Herman, R. C., and Wallace, G. B.: Proc. Soc. Exper. Biol. & Med. **35**:163, 1936.

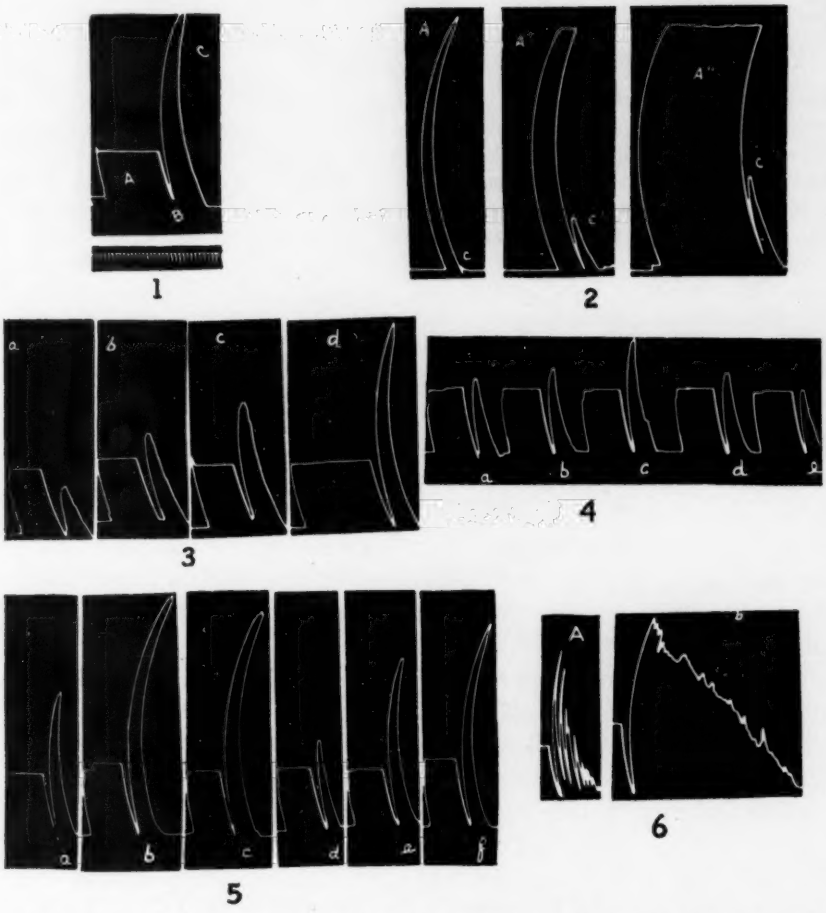

Fig. 1.—*1*, typical record showing (*A*) voluntary elevation of the leg, (*B*) voluntary relaxation and (*C*) involuntary after-contraction. The time is expressed in seconds. *2*, effect of prolongation of the stimulus. The preliminary contractions *A*, *A'* and *A"* record the voluntary elevation of the leg with no weight attached. The after-contraction, represented by *C*, *C'* and *C,"* respectively, is absent in the first record, increases in the second and is highest in the third. *3*, effect of load and duration of stimulus. In *a* the load was 1 Kg., and the duration, ten seconds; in *b* the values were 3 Kg. and ten seconds, respectively; in *c*, 5 Kg. and ten seconds, and in *d*, 3 Kg. and twenty seconds. *4*, effect of facilitation and fatigue on a series of after-contractions obtained consecutively with no delay between the cycles. The load was 3 Kg., and the duration, ten seconds. *a*, *b* and *c* show facilitation, and *d* and *e*, fatigue. *5*, effect of reenforcement (*a*) on normal after-contraction in the left leg, with a load of 3 Kg. and a duration of ten seconds; (*b*) with dorsiflexion of the left foot; (*c*) with the left arm lifting 2 Kg.; (*d*) with the right arm lifting 2 Kg.; (*e*) with each arm lifting 2 Kg., and (*f*) with the Jendrassik procedure. *6*, normal variations. (*a*) oscillatory type of after-contraction, with a load of 6 Kg. and a duration of fifteen seconds, and (*b*) prolonged clonic type of after-contraction, with a load of 3 Kg. and a duration of fifteen seconds.

All the figures are reduced one-half from the originals. The time record in *1* applies to all the records. In the records a height of 1 cm. corresponds roughly to a rotation of the leg through 10 degrees. (From Sapirstein, Herman and Wallace.[1]

Reenforcement of the after-contraction may be obtained in several ways. Contraction of a muscle group in the part undergoing the after-contraction (e. g., clenching the fist during abduction of the arm) causes the greatest reenforcement. Likewise, dorsiflexion of the foot of the extremity tested causes a marked increase in the after-contraction. In order to demonstrate that such reenforcement is not a purely muscular effect, it was shown that during an after-contraction in the leg muscular contraction in the ipsilateral arm causes marked reenforcement, whereas a similar muscular contraction in the contralateral arm frequently inhibits the phenomenon. The Jendrassik method (pulling the arms apart against resistance from the interlocked fingers) does not always augment the after-contraction, as it does the tendon reflexes; indeed, it frequently inhibits it (fig. 1, *5*).

The latent period, the interval between the voluntary relaxation and the subsequent involuntary after-contraction, is difficult to measure accurately with the procedure used here. In general, however, it is about one-fifth second, sometimes as long as two seconds or, with fatigue, even longer. If during this latent period voluntary and momentary tension of the extremity is made in the opposite direction, the after-contraction may be inhibited. Although the phenomenon may thus be checked and is amenable to the will, it frequently is so powerful as to be insuppressible. In several instances the after-contraction was so forceful that the subject could bring his leg down to the normal position only with considerable effort. In other cases when the leg was voluntarily brought down before cessation of the involuntary after-contraction, there was a second elevation of the limb.

Although the characteristics of the after-contraction of any one person are constant over a long period, individual variations are not uncommon. When the usual load of 6 Kg. and a time of support of ten seconds were employed, the duration of the after-contraction varied from three to forty seconds. With certain subjects the after-contraction was absent (although it could be brought out by practice, facilitation and reenforcement); in others it was the maximum movement anatomically possible. Most subjects have an after-contraction that lasts from eight to fifteen seconds, during which the leg rises about 30 degrees. In addition, there are differences in the performance, some being smooth and others jerky. It is interesting to note that some subjects whose after-contraction was visibly smooth remarked that it felt jerky or discontinuous (fig.1, *6*).

CLINICAL STUDIES

The evidence thus far adduced suggests that cortical after-discharge plays the most important role in the mechanism of after-contraction.

However, it was thought that studies along neurologic lines were necessary in order to determine whether other parts of the nervous system participate in the production of this automatic phenomenon.

In order to determine whether the proprioceptive sense is necessary for the production of after-contraction, patients with tabes dorsalis were studied. In all the 12 subjects investigated, the knee jerks were absent. Ten gave average, and 2 very small, after-contractions. No correlation could be found between the severity of the tabes and the amplitude of the after-contraction. It is believed therefore that the variation in the tabetic patients was no different than that ordinarily found in a similar

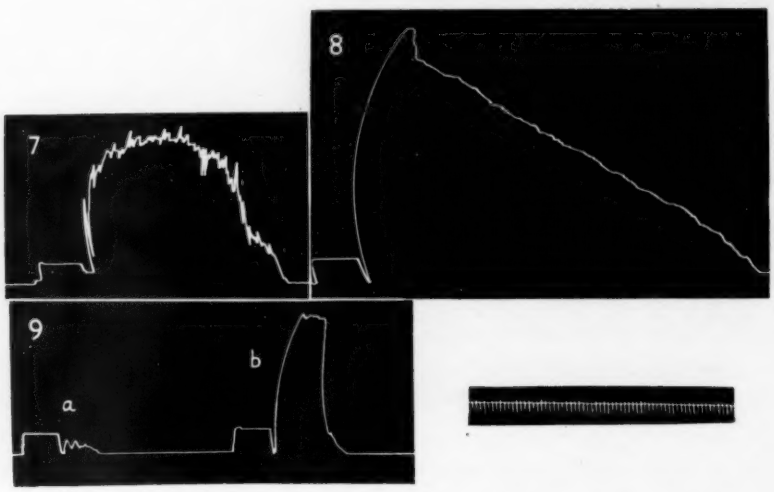

Fig. 2.—*7* is a tracing obtained from a patient with tabes dorsalis, illustrating the marked after-contraction which can be obtained in patients with this disease. The marked oscillation is occasionally found in normal subjects, but most tabetic patients give a smooth performance, similar to that shown in figure 1, *1*. The load was 3 Kg. *8* illustrates prolonged after-contraction obtained in a patient with paralysis agitans. The load was 6 Kg. *9* demonstrates the diminished after-contraction on the paretic side in a patient with hemiparesis. After-contraction on the paretic side is shown in *a*, as compared with that on the healthy side (*b*). Both legs lifted an initial load of 4 Kg. The time of stimulation was ten seconds.

All the figures are reduced to one-fourth the original size. The time signal (recording in seconds) applies to all records.

number of normal persons. It is noteworthy that several tabetic patients with ataxia gave marked oscillatory after-contractions. It is thought that in the main this phenomenon is independent of the deep muscle sense and is not related to the stretch reflex (fig. 2, *7*).

Some observers have maintained that the after-contraction has its origin in the basal ganglia or other extrapyramidal centers. Seven

patients with paralysis agitans exhibiting the typical features of extrapyramidal disease were studied; in most of them the after-contraction was forceful. Although the amplitude of the movement was within normal range, its duration was usually prolonged, sometimes lasting well over a minute (fig. *2, 8*). These patients all expressed the opinion that the long after-contraction was due not to the rigidity of the muscles but to something that they felt to be constantly pushing the limb. In some the tremor disappeared during the after-contraction, as during voluntary acts. The presence of after-contraction in the patients just mentioned indicates that the "extrapyramidal system" is not entirely necessary and that, in fact, its degeneration may lead to prolongation of the effect.

In order to investigate the cerebellum as a source of after-contraction, studies were made on a boy aged 12 with a congenital cerebellar syndrome. This syndrome, which had been present since early childhood, was caused by defective development either of the cerebellum or of its main pathways. No other part of the nervous system appeared to be affected. The reaction obtained was of great amplitude, but differed from the usual in that the rise was jerky. The subject commented that he felt as if his limb was being "pushed up by a crank" in a discontinuous manner. Patients with other cerebellar diseases, including cerebellar tumor, were studied, with similar results.

Disease of the pyramidal tracts was studied in an effort to determine what effect disease of cortical connections may have on the after-contraction. Patients with hemiplegia of long standing (with some return of strength in the affected limbs) were investigated for comparison of the healthy and the paretic side. To make the comparisons valid, the maximum load employed on the two sides was one which could be lifted by the leg on the paretic side. With this method it was found that the amplitude of the after-contraction was much less in the affected extremities, in which the tendon reflexes were hyperactive (fig. *2, 9*). It is noteworthy that the after-contraction is much smaller when the cortical innervation of the muscle is disturbed.

The fact that the after-contraction is much smaller on the side with hyperactive reflexes shows that there is no relation between spinal reflex irritability and after-contraction. The presence of a normal after-contraction in patients with tabes, whose tendon reflexes are absent, also points to this conclusion. In addition, no correlation could be found between after-contraction and tendon reflex irritability in normal subjects.

Thus, it seems that the cerebellum, the basal ganglia and the proprioceptive system are not sources of the after-contraction, although each may modify it in the same manner in which voluntary movements are affected.

COMMENT

Salmon,[3] one of the first to report this phenomenon, suggested that the after-contraction is of cortical origin. He based his contention on the relation of after-contraction (or as he termed it, *phénomène d'automatisme*) to the emotions and also on unilateral modifications which he observed in patients with certain nervous disorders. He stressed the analogy between after-contraction and after-image and suggested that as a result of energetic and prolonged initial voluntary contraction the resulting intense kinesthetic image persisted in the cortical centers after cessation of the original muscular effort. Kohnstamm [4] described the phenomenon under the heading *Nachbewegung (Katatonusversuch)* and likened it to catalepsy. His explanation was that when a set of muscles is extended and in a state of tension the muscles take on a new position of equilibrium (*Gleichgewichtslage*), to which they return as soon as freedom of movement is brought about by relaxation. He assumed that a special tonic innervation is responsible. Among other authors who reported on the after-contraction, Rothmann [5] expressed the belief that the reaction depends on continuation of subcortical impulses after cessation of the voluntary movement, the stimulus coming from the cerebellum. Csiky [6] compared the reaction to after-image and explained it as an idiomuscular contraction. Matthaei [7] agreed with Rothmann in ascribing the cause to the duration of excitation of subcortical centers. Pinkhoff [8] concluded that the spinal motor cells remain in a state of excitability after the primary stimulation, partly from the voluntary impulses causing the initial movement and partly from proprioceptive impulses arising in the muscles. As previously pointed out, the reasons advanced by these investigators are not adequate and are at variance with the facts presented here.

In the light of more recent work it is possible to consider the various functions of different portions of the nervous system and to evaluate the part each plays in the phenomenon of after-contraction.

Idiomuscular Apparatus.—Of those who have worked on the subject, Csiky alone contended that after-contractions are idiomuscular; he based this contention on his ability to obtain these movements by strong direct faradic stimulation of motor points on the arm. He admitted, however, that his results were variable, the after-contraction sometimes occurring in the opposite direction. Kohnstamm, Rothmann and Matthaei disagreed with his results, and it is probable that any after-con-

3. Salmon, A.: Rev. neurol. **23**:27, 1916.
4. Kohnstamm, O.: Neurol. Centralbl. **34**:290, 1915.
5. Rothmann, M.: Neurol. Centralbl. **34**:421, 1915.
6. Csiky, J.: Neurol. Centralbl. **34**:775, 1915.
7. Matthaei, R.: Arch. f. d. ges. Physiol. **202**:88, 1924; **204**:587, 1924.
8. Pinkhoff, J.: Arch. néerl. de physiol. **6**:615, 1922.

tractions Csiky may have obtained by this method were due to voluntary resistance to the movement caused by the current, which of itself involves prolonged cortical activity on the part of the subject. In addition, Csiky claimed that the long latent period (the period between the removal of the resistance and the subsequent rise of the limb) and gradual rise are incompatible with the view that the muscular movement is a result of the continuation of central nerve activity. The long latent period may indeed exclude the spinal, but not the higher, centers from the dominant role. Creed and others [9] showed that a supraliminal state of the spinal centers cannot exist but that continued discharges from the spinal cord must be due to continual charging. It is obvious that the slowly developing after-contraction cannot be due to a discharge of overstimulated anterior horn cells but must be related to a discharge from these cells dependent on a stimulus coming from cells above the level of the cord.

Other reasons that it is not believed that the after-contraction is idiomuscular are as follows: (*a*) the striking effects on the after-contraction of caffeine and other drugs, which are known to have negligible effects on muscle in the doses given; (*b*) the rapid onset of fatigue and facilitation, especially under the influence of drugs, which points to a more labile control; (*c*) the failure in experiments on animals to obtain any similar effect on stimulation of the distal end of a severed nerve, while after-contractions are easily obtained by central nerve stimulation,[10] and (*d*) the absence of any correlation with muscular strength.

Proprioceptive Pathways.—The reasons that these pathways must be excluded from an important role in initiation of after-contraction are as follows: (*a*) After-contractions are present in tabetic persons, despite the absence of proprioceptive reflexes; (*b*) bromides, which depress the after-contractions completely, do not affect the proprioceptive reflexes in the doses given, and (*c*) in patients with hemiparesis the after-contractions are smaller on the side on which the lower reflex arcs are most active.

Spinal Cord.—The following arguments point strongly against a spinal origin: 1. The long intervals involved in the after-contraction, such as the latent period and the long duration (as much as forty seconds) of residual tension, are incompatible with most spinal reflexes. 2. As has already been pointed out, a supraliminal state is absent in the spinal cord; that is, there must be constant charging if the spinal

9. Creed, R. S., and others: Reflex Activity of the Spinal Cord, New York, Oxford University Press, 1932.

10. Liddell, E. G. T., and Sherrington, C. S.: Proc. Roy. Soc., London, s.B **95**:299, 1923.

centers continue to discharge. Since the observations on tabetic patients exclude the proprioceptive sense as a necessary factor, the charging impulses must come from higher centers. 3. Strychnine and chloral hydrate, both of which affect the spinal cord, have a negligible influence on the after-contraction. 4. Spinal tendon reflexes can be elicited when the after-contraction has disappeared under the influence of small doses of bromides. 5. Jendrassik reenforcement has a variable effect on the after-contraction, although it almost always increases the amplitude of spinal reflexes. 6. In cases of hemiparesis, on the side in which the spinal tendon reflexes are increased the after-contraction is decreased. 7. There is no relation between the after-contraction and muscle tone, for in cases of cerebellar disease and tabes, in which there is hypotonia, the after-contraction can be elicited easily. On the other hand, in cases of paralysis agitans, in which there is rigidity, the after-contractions can also be elicited easily. However, in cases of disease of the pyramidal tracts, in which there is spasticity, the after-contractions can be obtained only with great difficulty.

Subcortical Centers.—It is concluded that these centers do not furnish the necessary sources of the after-contraction, for these reasons: (*a*) The after-contractions are prolonged in cases of paralysis agitans, in which the subcortical motor centers are affected, and (*b*) the results with the drugs cited are not in accord with such a conclusion.

Cerebellum.—The fact that the reaction has been obtained in cases in which the disease is accompanied by loss of cerebellar function, as well as numerous other arguments to be presented, precludes the possibility of a cerebellar source.

Cortex.—The cortex or some of its projection systems are suggested as the site of origin of the after-contraction. The arguments are as follows: 1. Striking effects are obtained with bromides in doses which do not act on tendon reflexes. 2. The effect of caffeine is that of a cortical stimulant. 3. After-contractions have been reported to disappear in cases of dementia paralytica.[4] 4. Similar movements are elicited from the cortex by electrical stimulation. Graham-Brown and Sherrington[11] showed that two types of after-discharge, tonic and epileptiform, originate in the cortex. Both these types of after-contraction are found in various normal persons. 5. Facilitation of a type similar to that described by Graham-Brown as coming from the cortex may be observed in after-contraction.[12] 6. The long latent period and the great duration of the after-contraction are not compatible with origin from lower centers. Graham-Brown and Sherrington[11] showed that

11. Graham-Brown, T., and Sherrington, C. S.: Proc. Roy. Soc., London, s.B **85**:250, 1912.

12. Graham-Brown, T.: Quart. J. Exper. Physiol. **9**:131, 1915.

long latencies are typical of cortical discharges. 7. Similar uncontrollable movements, such as jacksonian fits, may emanate from the cortex. 8. In cases of disease of the pyramidal tracts, in which cortical connections are involved, the after-contractions are diminished on the affected side. 9. The effects of reenforcement on the after-contraction closely parallel cortical spread under direct stimulation.

It has been shown that stimulation of a point on the motor cortex stimulates the activity of nearby cortical centers. As has been mentioned, powerful contractions of ipsilateral muscles, even though not in the same extremity, always augment the after-contraction. This reenforcement is probably due to spread of the cortical stimulus from the nearby point. On the other hand, similar muscular contractions on the opposite side frequently inhibit the after-contraction. This inhibition of the after-contraction by contractions of contralateral muscles is interesting in the light of observations by Wechsler, Bieber and Balser,[13] which showed that contractions of contralateral muscle groups can inhibit jacksonian seizures.

The characteristics of the after-contraction correspond to those of after-discharge studied in the experimental animal. It has been shown that they are modified by the same influences and that the after-contraction closely simulates the after-discharges arising from the cortex.[1]

The persistent excitatory state in the cortical neurons seems to be the important factor in the development of after-contraction. The involuntary movement is, in fact, a replica of the coordinated voluntary movement necessary to produce it. It brings into association widely scattered areas of the nervous system, each capable of exercising an influence on the final result, as in voluntary movement. Of necessity, the cortical excitatory state shown to occur in the after-discharge following direct cortical stimulation must also be present in the after-contraction following conscious stimulation.

APPLICATIONS

We believe that the after-contraction has a field of usefulness in the study of the nervous system. It affords a simple method whereby at least parts of the nervous system can be investigated with ease in an intact animal (man). If, as we suggest, the after-contraction is chiefly a function of the cortex or its projection pathways, there is at hand a comparatively simple, yet effective, method for studying certain functions of the nervous system. It is noteworthy how readily such phenomena as reenforcement, facilitation and inhibition may be demonstrated by

13. Wechsler, I. S.; Bieber, I., and Balser, B. H.: Postural Reflexes in Patients with Lesions of the Frontal Lobe, Arch. Neurol. & Psychiat. **35**:1208 (June) 1936.

means of after-contraction. This method not only is simpler than that involving experimental animals but is directly applicable to man under ordinary conditions. That which it loses by not being as well controlled as other experimental procedures it gains by ease of interpretation, since the work is conducted without anesthesia or operative procedure. Many of the physiologic phenomena demonstrated with experimental animals have already been paralleled by means of after-contraction. Furthermore, the study of after-contraction demonstrates the role that the cortex plays in the control of involuntary muscular tension. In addition to being a useful tool in physiologic investigation, it has proved an effective means for the study of drugs.

Thus, drugs commonly used as depressants (bromide, phenobarbital) in the management of epilepsy diminish the after-contraction; it may be possible to investigate the effect of drugs on epilepsy by a study of their effect on the after-contraction. Experimental investigations along these lines now in progress will be reported on a future occasion. At present, the usefulness which this method of investigation may have in neurologic and psychiatric research can only be inferred.

Thus far, no correlation has been made between the after-contraction and psychologic factors. The great individual variability of the reaction may have some psychologic significance. It has been suggested that in general the after-contraction can be correlated with the "affect" of the subject, apathetic persons giving little or no reactions. The ease with which the after-contraction may be facilitated by repeated performance and the fact that it appears to increase, up to a certain point, with practice suggest that the phenomenon may be a factor in the training of motor habits. It is possible that many actions of everyday life which have been described as "psychologic" may be explained by after-contraction.

An experiment carried out by Fechner[14] on weight lifting is of interest in this connection. He described how the weights lifted toward the end of a series appeared to be lighter than those at the beginning. One might explain this effect on the basis of after-contraction. With each succeeeding weight there is an increased amount of after-contraction, depending on increased motor cortical excitability. When the final weights in the series are lifted, the force due to the after-contraction becomes a significant fraction of the total force necessary to lift the load. This after-contraction is purely involuntary and therefore requires less subjective effort. This explanation of Fechner's experiment is based on the phenomenon of the facilitation of after-contraction.

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14. Fechner, G. T.: Abhandl. d. math.-phys. Kl. d. säcks. Gesellsch. d. Wissensch. **12**:76, 1860.

It is possible that after-contraction may have bearing on acts even more complicated than those involved in Fechner's experiment. The long-standing custom of preliminary activity for athletic performance with excess weights, such as a baseball player's warming up with several bats or a runner's practicing with heavy shoes, may not be entirely explainable on the basis of the "psychologic" state, "opening up new pathways" or "toning up the muscles." In such instances the use of excess weight increases cortical motor excitability. With constant repetition the cortical areas may remain at this point of excitability, and less voluntary effort is then necessary to initiate the discharges needed to achieve the desired muscular effect. This suggestion is based on the facts that: (*a*) after-contractions may be forceful; (*b*) they may be facilitated, and (*c*) they may be long lasting with practice.

How far one may utilize the concept of after-contraction in studies of ordinary motor learning we shall not say. We venture, however, to make a suggestion concerning the importance of after-contraction. Before doing so, we wish to emphasize the fact that for the production of after-contraction a large initial stimulus produced by external forces is not necessary. Supporting the weight of the limb itself is sufficient. In walking or running there is a repetitive movement, perfectly coordinated, which eventually is made with almost no conscious effort; indeed, the movement seems entirely automatic. It is easily believable that a basic factor involved here is that represented by after-contraction, which is a sustained cortical excitatory state responding in a rhythmic fashion to stimuli of which the subject is unconscious and which is developed according to the mechanisms already discussed.

SUMMARY

After-contraction is the involuntary movement which follows prolonged muscular contraction in man. It may be elicited when any set of muscles is voluntarily kept in action for a time against resistance. After relaxation of the contracting muscles and subsequent removal of the resistance, there usually follows an involuntary repetition of the originally intended movement, accompanied by a sensation of lightness or floating upward of the part.

This phenomenon, which has received various explanations, has been reinvestigated in the light of more recent advances in the physiologic action of the nervous system. Pharmacologic studies have demonstrated the pronounced effects of bromide and caffeine on the phenomenon and the relative absence of any action of such drugs as strychnine and chloral hydrate. Physiologically, the after-contraction is influenced by facilitation, fatigue and changes in initial load and duration of effort. The phenomenon is always reenforced by simulta-

neous contraction of ipsilateral muscles and is frequently inhibited by contraction of contralateral muscles. Clinical studies have shown that a relatively normal reaction is associated with tabes and cerebellar syndromes, a prolonged after-contraction with paralysis agitans and a diminished response with disease of the pyramidal tracts.

It is concluded that the after-contraction is mainly an after-discharge from the cortex or its projection pathways. It is modified by other parts of the nervous system, as is voluntary activity. Suggestions are offered concerning the usefulness of after-contraction as a method of investigating the physiologic behavior of the cortex and of studying drugs used in controlling its excitability. Theoretical views are advanced as to the possible role of after-contraction in habit formation.

Dr. G. B. Wallace, professor of pharmacology of the New York University College of Medicine, assisted in the experiments and made numerous suggestions. The members of the department of neurology of the Bellevue and Montefiore Hospitals placed patients at our disposal.

INTERCELLULAR SUBSTANCE OF THE CEREBRAL CORTEX (NISSL'S CEREBRAL GRAY MATTER)

PHYSIOLOGIC SIGNIFICANCE

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Nissl [1] deplored the fact that after the appearance of the neuron theory and the demonstration of the Golgi apparatus interest in the intercellular substance of the brain practically disappeared and that in the textbooks of the day it was mentioned briefly, if at all. In the same vein, Spielmeyer [2] said that there was still no possibility of demonstrating histologically the Nissl gray matter. At that time it was generally conceded that there is something in the gray substance of the central nervous system besides ganglion cells and their processes, neuroglia cells and blood and lymph vessels, since the spaces between these elements are not entirely filled.

Meynert,[3] among others, maintained that there is a substance in the cortex of the brain independent of the nerve components and that the nerve cells and their processes alone do not give the picture of the gray substance. He observed that the intercellular substance is increased in the cortex of animals of higher development and in the human brain and in the frontal and precentral regions. This substance has been variously described as homogeneous, glassy, granular, fibrillar, horny and spongy.

At present little relating to the cerebral intercellular substance appears in the literature concerning the brain. Textbooks rarely mention this material. In view of all this, it is my intent in this paper to demonstrate that this substance can be studied microscopically and with sufficient accuracy to give it importance in the field of pathology, as well as elsewhere.

This work was done in the laboratory of the psychopathic ward of the Philadelphia General Hospital.

The investigation was aided by a grant from a fund from the Gladwyne Research Laboratory, obtained through Dr. S. D. Ludlum.

1. Nissl, F.: Die Neuronenlehre und ihre Anhänger, Jena, Gustav Fischer, 1903.

2. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922; Ergebn. d. Neurol. u. Psychiat. **1**:217, 1912.

3. Meynert, T.: Psychiatrie: Klinik der Erkrankungen des Vorderhirns, Vienna, W. Braumüller, 1884, p. 52.

The subject of intercellular substance in general has had some degree of attention, though its problems are not entirely settled.[4]

Both Cowdry [5] and Maximow [6] spoke of intercellular substance as "cement substance," thus implying that its function is similar to that of mortar in building materials. Cowdry [7] also mentioned protoplasmic bridges, which he said may be artefacts or indications of a fibrous structure of the intercellular "cement" or both. Cajal [8] assumed the existence of an intercellular substance and recognized its presence in the brain.

Bremer [9] recently gave a full description of general intercellular material. He said that as a result of their own protoplasmic activity the cells of many tissues become surrounded by some sort of intercellular substance, which may be solid or fluid. When present in small amount it forms a thin layer of cement substance between closely adjacent cells. In large amounts these substances constitute a groundwork in which the cells are embedded, as in cartilage and bone. Alfejew [10] spoke of the embryonal histogenesis of an amorphous intercellular substance.

EMBRYOLOGIC DEVELOPMENT

In 1897 Hammar [11] observed that the first line of cleavage does not cut through the cell; the dividing cleft of the first two blastomeres plainly arises intraplasmatically, and this is true as the cells continue to divide. In embryos of selachians Studnicka [12] observed a ground substance between not only single cells but entire cell layers. Aschoff,[13] in citing Ranke, said that in development the cells wander into a gelatinous, cell-free material, which must be a product of cells. He expressed his personal opinion that the pathologic changes in the inter-

4. Mallory, F. B., and Parker, F., Jr.: Am. J. Path. **3**:515, 1927. Bensley, S. H.: Anat. Rec. **60**:93, 1934. Schaffer, J., in von Möllendorff, W.: Handbuch der mikroscopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, vol. 2, pt. 2, p. 1.

5. Cowdry, E. V.: General Cytology, Chicago, University of Chicago Press, 1924; Textbook of Histology, Philadelphia, Lea & Febiger, 1934, p. 370.

6. Maximow, A. A., and Bloom, W.: Textbook of Histology, ed. 2, Philadelphia, W. B. Saunders Company, 1934, p. 29.

7. Cowdry, E. V.: Special Cytology, ed. 2, New York, Paul B. Hoeber, Inc., 1932, p. 6.

8. Ramón y Cajal, S.: Manual de histología normal y de técnica micrográfica para uso de estudiantes, ed. 5, Madrid, N. Moya, 1910, p. 119.

9. Bremer, J. L.: Lewis and Stöhr's Textbook of Histology, ed. 4, Philadelphia, P. Blakiston's Son & Co., 1930, p. 18.

10. Alfejew, S.: Ztschr. f. Zellforsch. u. mikr. Anat. **3**:149, 1925-1926.

11. Hammar, J. A.: Arch. f. mikr. Anat. **49**:92, 1897.

12. Studnicka, F. K.: Anat. Anz. **31**:497, 1907.

13. Aschoff, L.: Arch. per le sc. med. **50**:21, 1927.

cellular substance are an important factor in the whole pathologic picture and that they are too little considered in textbooks.

Baitsell [14] worked at length on this subject; his results agreed with those of Szily that the presence of a primitive ground substance is demonstrable before the appearance of the mesenchymal cells. Differential stains have shown plainly the boundaries of the cell protoplasm. Many earlier writers [14a] agreed that the intercellular substance was derived from living cells. More recently (1935), Peters [15] stated that there can be no question of the existence of an intercellular substance which is greatly hydrated.

INTERCELLULAR SUBSTANCE OF THE BRAIN

Little of recent origin concerning the special intercellular substance of the cortex of the brain is to be found in the literature. My interest has extended over a long time, and the study of this material has been carried on by a variety of means. Some of the earlier work has already been reported.[16]

PRESENT INVESTIGATION

With the dark field microscope it is possible to examine fresh brain tissue and to see its structure. Fresh cortical tissue of the albino rat has been used, as well as unfixed human material obtained post mortem. The appearance of the intercellular substance of the cerebral cortex suggests that of a finely divided substance which has taken up a large amount of water, giving it the consistence which results from cooking fine meal until it has become thick and glutinous.

After a prolonged experiment on the precipitation of serum (blood) proteins with alcohol, it appeared that there is a close analogy between blood serum and the intercellular substance in general. This has been investigated in particular with relation to the intercellular substance of the brain.

In his textbook, Mathews [17] used the chapter heading "Blood, the Circulating Tissue." Cajal [8] sustained this point of view in his state-

14. Baitsell, G. A.: Am. J. Anat. **28**:447, 1921; Quart. J. Micr. Sc. **69**:571 1924-1925.

14a. Heidenhain, M., and others: Plasma und Zelle, Jena, Gustav Fischer, 1910.

15. Peters, J. P.: Body Water: The Exchange of Fluids in Man, Springfield, Ill., Charles C. Thomas, Publisher, 1935, p. 92.

16. Taft, A. E., and Ludlum, S. D.: J. Nerv. & Ment. Dis. **70**:360, 1929. Ludlum, S. D.; Taft, A. E., and Nugent, R. L.: Histology of the Nervous System: Some Observations with Ultramicroscope, Arch. Neurol. & Psychiat. **23**: 1121 (June) 1930.

17. Mathews, A. P.: Textbook of Physiological Chemistry, ed. 4, Baltimore, William Wood & Company, 1925, p. 474.

ment that blood plasma corresponds to the intercellular substance of other tissues.

The likeness in appearance of precipitated (aggregated) blood serum and the intercellular substance of brain tissue, as seen in the dark field, is striking (fig. 1). In order to render visible the individual micelles, which make up the colloidal solution of which blood serum and the intercellular substance of the cerebral cortex consist, various methods were tried, one of which resulted in a degree of success. This consisted in simple drying at room temperature, without fixatives, of thin films of brain tissue (human) and a smear of blood serum (human). Their close resemblance is clearly demonstrable (fig. 2).

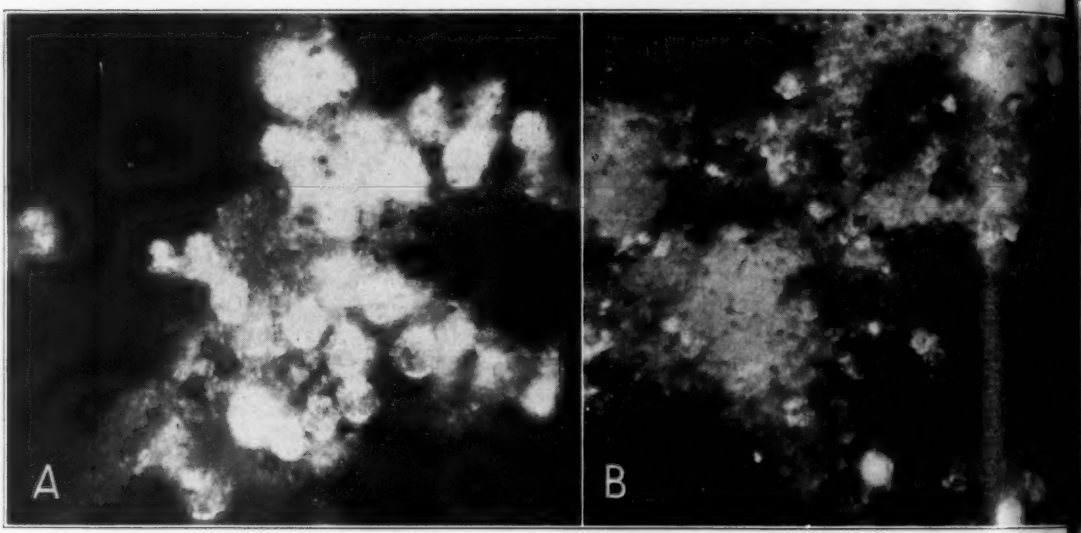

Fig. 1.—Dark field photographs (oil immersion lens) of (*A*) brain tissue and (*B*) an alcoholic precipitate of serum; × 970.

This is of special interest because the physicochemical properties of blood serum are well known. The physiologic significance of the serum proteins has been demonstrated, and their alterations in pathologic conditions have been established.

PATHOLOGIC CHANGES

From their own work, Nissl and Alzheimer[18] found that it was necessary to consider the reaction of the tissue surrounding the altered

18. Nissl, F., and Alzheimer, A.: Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten, Jena, Gustav Fischer, 1904, vol. 1, pp. 314 and 435.

cells in order to understand the nature of pathologic changes in the nerve cells.

Concerning the pathologic alterations in intercellular substance in general, the work of Wolbach and his associates [19] is of interest. They observed that the outstanding lesion in scurvy is loss of power to produce intercellular substance. This was also demonstrated by Aschoff and Koch,[20] and later by others as well.[21] The dramatic appearance of the beginning formation of intercellular substance within a very short time after the administration of antiscorbutic treatment indicates the dependence of such formation on the presence of a sufficient amount of vitamin C, the antiscorbutic vitamin.

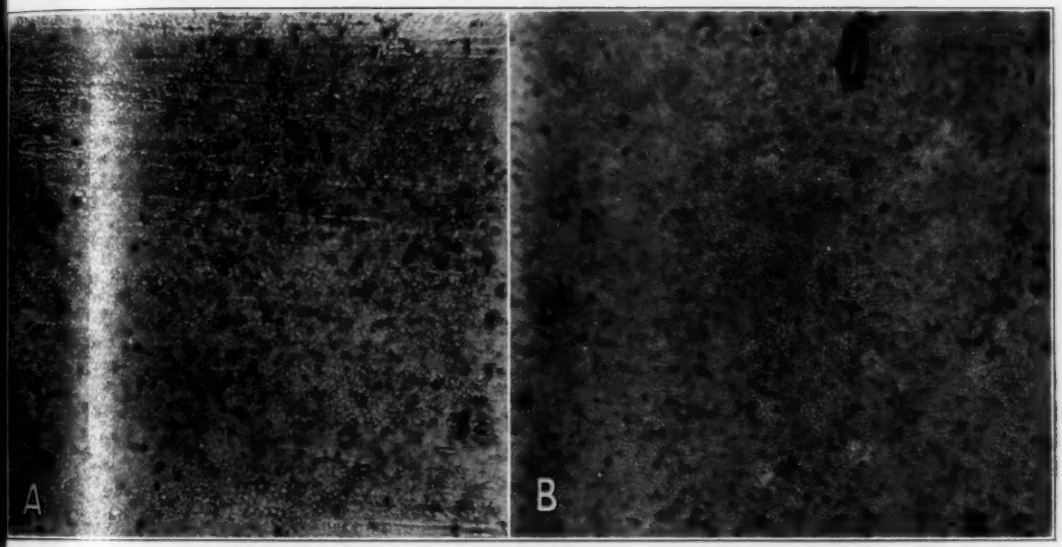

Fig. 2.—*A*, a dried film of brain tissue, showing the individual particles of the intercellular substance, and *B*, a similar preparation of natural blood serum, showing the finely granular nature of the colloid protein; × 970.

In a dark field study of the cortical tissue from varied pathologic material, I observed that a marked change in the intercellular substance of the brain, notably in association with dementia paralytica, was con-

19. Wolbach, S. B., and Howe, P. R.: Intercellular Substances in Experimental Scorbutus, Arch. Path. **1**:1 (Jan.) 1926. Wolbach, S. B.: Am. J. Path. **9**:689, 1933; New England J. Med. **215**:1158, 1936.

20. Aschoff, L., and Koch, W.: Skorbut: Eine pathologisch-anatomische Studie, Jena, Gustav Fischer, 1919.

21. Aschoff, L., and Koch, W.: Veröffentl. a. d. Geb. d. Kriegs- u. Konstitutionspath. **1-2**:1, 1921. Böger, A., and Schröder, H.: Klin. Wchnschr. **13**:842, 1934. Ingalls, F. H.: New England J. Med. **215**:1279, 1936.

spicuous. This presents a point of interest, since it is generally conceded that the treatment of dementia paralytica does not directly affect the infecting organism. The classic picture of the brain in dementia paralytica before early treatment was given so generally was gross atrophy of the frontal portion of the cortex and, microscopically, marked disturbance of the cellular lamination, sometimes described as presenting a "wind-blown" appearance.[22]

Spielmeyer described disturbance of the cortical layers and notable thinning of the intercellular substance through loss of its finer constituents as the most important change in the general histologic picture of the cortex associated with dementia paralytica. Nissl and Alzheimer [23] also reported disappearance of the Nissl gray substance of the cortex in cases of dementia paralytica. Change in the intercellular

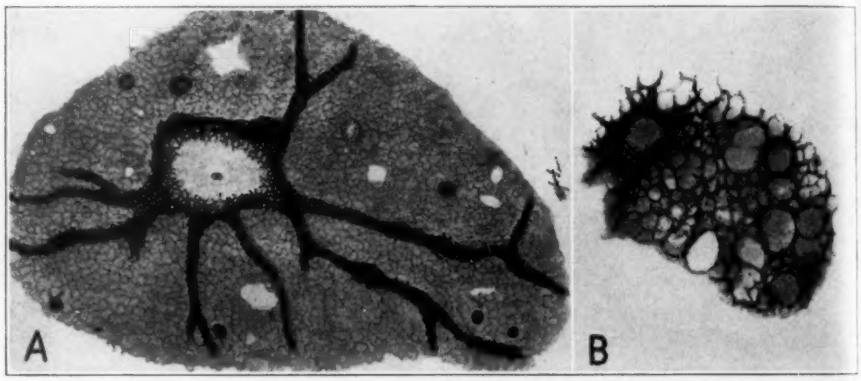

Fig. 3.—Fixed and stained tissue showing the intercellular substance in (*A*) the normal brain and (*B*) the brain of a patient with dementia paralytica (after Belloni).

substance of the brain in association with dementia paralytica has more recently been studied, described and photographed in fixed and stained sections by Belloni,[24] who demonstrated that there is a striking lesion in the intercellular substance (fig. 3).

Also of interest in this relation is the work of Plaut and von Bülow,[25] who examined the spinal fluid for the presence of vitamin C in relation to the malarial treatment of dementia paralytica. Their results showed that the amount of the vitamin fell during the period of fever, but

22. Freeman, W.: Neuropathology: The Anatomical Foundation of Nervous Diseases, Philadelphia, W. B. Saunders Company, 1932, p. 200.

23. Nissl and Alzheimer,[18] p. 18.

24. Belloni, G. B.: Riv. di neurol. **5**:81, 1932.

25. Plaut, F., and von Bülow, M.: Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:324, 1935; **153**:182, 1935.

increased from five to eight weeks later to a level above that preceding treatment. They also examined brain tissue and found a greater amount of vitamin C in the cortex of the normal brain than elsewhere. More was present in the gray than in the white matter until in advanced age, when the proportion was reversed. This suggests a parallel with the intercellular substance in the cortex of the brain. It has recently been reported by Castrovilli [26] that the administration of vitamin C in the treatment of malaria favors recovery notably.

Wortis, Wortis and Marsh contributed to information on this subject in their report that alcoholic persons showing mental and nervous symptoms were found to have an abnormally low vitamin C content of the blood and spinal fluid, while alcoholic persons free from such symptoms showed normal amounts of vitamin C.

PHYSIOLOGIC FUNCTIONS

The importance of the intercellular substance of the brain rests largely on its physiologic function. If the analogy with the serum proteins is continued here, the function of the intercellular substance of the cortex is that of a mediator between the blood and the lymph, on the one hand, and the brain cells, on the other. According to the work of Clark and Clark,[27] there are no lymphatics in the brain. Nevertheless, a similar fluid may be present without definite vessels.

Cannon [28] described lymph as streams of water which take food, water and oxygen from the moist surfaces of the body to the cells in the remotest parts of the organism and bring back from the cells the useless waste to be discharged. Bayliss [29] compared the composition of lymph with that of blood—without corpuscles and with less protein. He mentioned filtration into tissue spaces. Cowdry [30] spoke of lymph as the aqueous environment of cells, composed of water, blood proteins, extractives and inorganic salts, coagulating like blood but more slowly.

COMMENT

To one who has worked with fresh brain tissue in the dark field, the presence of an intercellular substance, such as that described and shown in the illustrations, seems to be a certainty. Functionally, it appears to be an absolute necessity in order to maintain the integrity of the cortical

26. Castrovilli, G.: Minerva med. **1**:279, 1937.

27. Clark, E. B., and Clark, E. L.: Am. J. Anat. **52**:273, 1933.

28. Cannon, W. B., cited by Cowdry.[30]

29. Bayliss, W. M.: Principles of General Physiology, ed. 4, London, Longmans, Green & Co., 1924, p. 165.

30. Cowdry, E. V.: Human Biology and Racial Welfare, New York, Paul B. Hoeber, Inc., 1930.

brain cells. These cells are extremely fluid, and if they are floated out from their natural embedding material the cytoplasm undergoes rapid lysis, leaving the naked nucleus. The cells appear to have a degree of fluidity closely approximating that of the polymorphonuclear leukocytes, as seen in the dark field. Although not all the cells react alike in this respect, many undergo cytolysis in the usual physiologic solutions and in some specimens of blood serum.

It would be an exception to the means of natural protection if the cells of the cerebral cortex were not provided with some means of defense against too great hydration. Blood corpuscles have such protection in the serum proteins, and the eggs of fish, frogs and other forms which are deposited in water are provided with a matrix of similar gelatinous substance. This is true also of the ova of the rat, as shown by the work of Defrise [31] in artificial culture. He said that when the fallopian tube of the rat is incised there emerges a mucilaginous cloud containing the eggs.

In the serial literature and in books on cytology one sees frequent reference to tissue spaces. This does not always imply the recognized spaces lined with endothelium. Sabin [32] described small spaces between fibers and cells of connective tissue and between the parenchyma of organs and the supporting tissue, by which fibrous connective tissue is apparently meant. However, individual cells cannot, of course, be surrounded by spaces and thus occur as loose aggregates in the various organs. If one follows the evidence presented here, it will appear that there is some kind of intercellular substance present everywhere.

Lewis [33] questioned whether the adhesive quality of cells in tissue cultures is not dependent on the composition of the protoplasmic surface membrane or on some substance which is secreted by the cells as a product of their metabolism. He suggested that the so-called cement commonly described as existing between cells may be an adhesive substance. This suggestion corresponds with my observations and presents an answer to the question. In the capillaries of the rat brain it has been possible to observe clearly a delicate layer of intercellular substance in the walls of the capillaries by means of an agent which alters the water content, thus changing the degree of refraction sufficiently to render the substance visible in the dark field of the microscope. This is of interest in considering the work already referred to which has been done on the intercellular substance in cases of scurvy, since the clinical test for scurvy is the measurement of capillary resis-

31. Defrise, A.: Anat. Rec. **57**:239, 1933.

32. Sabin, F.: The Method of Growth of the Lymphatic System, in Harvey Lectures, 1915-1916, Philadelphia, J. B. Lippincott Co., 1917, p. 124.

33. Lewis, W. H.: Anat. Rec. **23**:387, 1922; **26**:15, 1923.

tance. Also, in relation to the intercellular substance of the brain it is of interest that scurvy is most frequent in infants and persons with psychoses.

When the evidence is considered, it appears that the intercellular substance in general is functionally not merely a "cement substance" serving to keep cells in their relative positions but a more active means for the distribution of body fluids, especially for circulation of the lymph stream in the brain. The substance must act as a safeguard for the brain cells in maintaining an osmotic equilibrium; otherwise, if tissue fluid came in direct relation with the cells themselves, they would be unable to maintain their integrity; since, however, they are surrounded by a substance such as that described, which absorbs water easily and gives it up with equal facility to maintain a state of osmotic equilibrium, their normal function is assured. This suggests the work of Schade [34] on the compensatory swelling and shrinking of cells and connective tissues.

On this basis, it is not difficult to understand many pathologic appearances in nerve cells, as well as their consequent clinical manifestations.

The mental and nervous reactions of infancy and old age may well depend on the fact that in the former the intercellular substance is not yet developed [24] and in the latter its formation is decreased or its ability to hold water is lessened, with the result that the general appearance of atrophy with marked narrowing of the cortex is produced.[35]

CONCLUSION

There is an intercellular substance in the cortex of the brain, the physical and physiologic characteristics of which are analogous in part to those of the serum proteins. In this respect, it acts not only as a purveyor of tissue fluid to and from the brain cells but as a control over the osmotic forces between the cells and the fluid in the brain. In addition, it furnishes an embedding material for the cortical cells and is altered in pathologic conditions (notably dementia paralytica), leaving the cells without normal protection. It may be of particular importance in connection with scurvy, in which the general intercellular substance is seriously involved. It is decreased in amount in brains of the newborn and the aged.

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34. Schade, in Alexander, J.: Colloid Chemistry, New York, D. Van Nostrand Company, Inc., 1919, vol. 2, p. 629.

35. Rothschild, D.: Am. J. Psychiat. **93**:757, 1937.

MORO REFLEX AND STARTLE PATTERN

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AND

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The Moro reflex, reported by Moro [1] in 1918, is a complex response in which the arms are extended at the sides to approximate an arch and then slowly brought together one over the other in front of the body. The legs execute a similar movement. It is found only in very young infants and has usually disappeared by the end of the fourth month. The stimulus most commonly used to elicit it is a sudden blow on the bed or table on which the infant is supported. Other stimuli, such as tapping the abdomen, extending the legs at the hips, blowing on the face,[2] cold or warm applications to the trunk and sudden movement through space,[3] will also elicit the response. Moro, stressing the second, "clasping" phase of the reflex rather than the primary extension, saw in this behavior a primitive, atavistic response the purpose of which is to enable the infant to clasp and cling to the mother. The Moro response is consequently referred to as a clasping reflex or *Umklammerungsreflexe,* and is considered to be adaptive in nature.

In the course of his investigation of the bodily behavior following a sudden loud sound (revolver shot), Strauss [4] reported that younger infants respond with the Moro reflex while older infants do not give this response but show the typical adult behavior pattern consisting of closing the eyes, moving the head, raising and bringing forward the shoulders, abducting the lower part of the arms, clenching the fists, moving the trunk forward, contracting the abdomen and bending the knees. Landis and Hunt verified Strauss's findings and called the

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1. Moro, E: Das erste Trimenon, München. med. Wchnschr. **42**:1147, 1918.

2. Schaltenbrand, G.: Normale Bewegungs- und Lage- reaktionen bei Kindern, Deutsche Ztschr. f. Nervenh. **87**:23, 1925.

3. Freudenberg, E.: Der Morosche Umklammerungsreflexe und das Brudzingskische Nackenzeichen als Reflexe des Saüglingsalters, München med. Wchnschr. **68**:1646, 1921.

4. Strauss, H.: Das Zusammenschrecken, J. f. Psychol. u. Neurol. **39**:111, 1929.

response the "startle pattern."[5] Strauss concluded that in very young infants a sudden loud sound will elicit the Moro reflex but that as the infant develops the Moro reflex disappears, to be followed by the startle pattern. A further investigation of a group of 60 infants by Hunt, Clarke and Hunt[6] verified Strauss's results, but cast doubt on his belief that the startle pattern does not appear until the Moro reflex has disappeared. The authors suggested two alternatives: first, that the two responses are present at birth, with the lesser startle pattern concealed at first by the grosser Moro reflex, and, second, that the startle response is merely a perseveration of the Moro reflex in a degenerate or decayed form. No choice was made between these alternatives.

Further experimental work by us, however, has shed light on the relation between these two responses. While a sudden loud sound remains the best stimulus, it is also occasionally possible to elicit the startle pattern in infants by a sudden puff of air on the face, the sudden turning up of photographic lights, the jab of a pin or a slap on the bed on which the infant is lying. Hence, the startle pattern is not solely an auditory reflex but a response to a sudden, intense stimulation. The careful use of ultrarapid photographic methods[7] has also revealed the frequent appearance of both the startle pattern and the Moro reflex in younger infants in response to one and the same stimulus. While elicitation of the Moro reflex is the rule in newborn infants, we have not observed a complete startle response before the age of 6 weeks, although fairly complete responses may appear before this. Occasionally we have observed the appearance of the startle response and the Moro reflex together at this age. As the child grows older the frequency in appearance of the startle pattern increases, while that of the Moro reflex becomes less. The period of overlap seems to end at the age of about 3 or 4 months, when the Moro reflex has disappeared and the startle pattern is well established. The startle pattern is rapid[8] and precedes the slower Moro reflex. The Moro response is not always preceded by the startle pattern. Some stimuli seem better adapted to produce the Moro reflex than the startle pattern. Probably the more sudden and intense the sitmulation the greater the chance that the startle pattern will appear. The difficulty in equating stimuli for "suddenness"

5. Hunt, W. A., and Landis, C.: Studies of the Startle Pattern: I. Introduction, J. Psychol. **2**:201, 1936; II. Bodily Pattern, ibid. **2**:207, 1936; III. Facial Pattern, ibid. **2**:215, 1936.

6. Hunt, W. A.; Clarke, F. M., and Hunt, E. B.: Studies of the Startle Pattern: IV. Infants, J. Psychol. **2**:339, 1936.

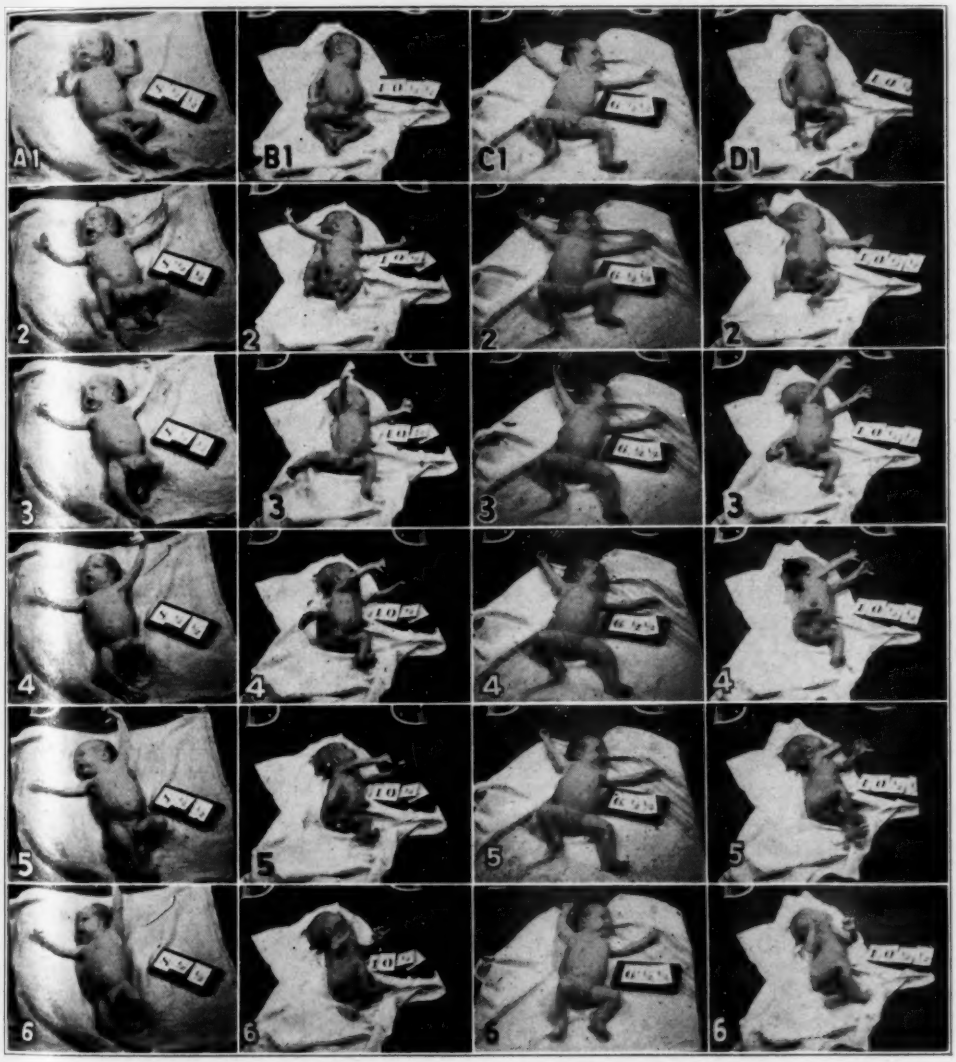
7. Landis, C., and Hunt, W. A.: Magnification of Time as a Research Technique in the Study of Behavior, Science **85**:284, 1937.

8. Landis, C., and Hunt, W. A.: Studies in the Startle Pattern: VI. Temporal Relations, J. Psychol. **3**:487, 1937.

and "intensity" and the danger in cross modality comparisons render the last statement speculative. There remains no doubt that one and the same stimulus may sometimes call forth both responses. Furthermore, while the Moro reflex gradually disappears, the startle pattern is at first somewhat irregular and becomes more definite as the infant grows older.

More careful examination of the Moro reflex casts doubt on Moro's interpretation of it as an adaptive, clasping response. The reflex really consists of two parts, comprising essentially opposed movements. In the first part, immediately after the stimulus there is stretching of the trunk; the head is tilted backward, and there are abduction and extension of the arms and extension of the hands and fingers. Sometimes this is accompanied by tremor in the arms. In the second part of the reaction (slow motion analysis shows a definite interval between the two phases), the arms are flexed and slowly brought together before the chest. Moro, choosing to concentrate on the second phase, assumed that he was dealing with a clasping response. If the second phase of the response is the more important one may well ask why it is the first to disappear in the genetic development of the child. The first movement of extension may be found to persevere in the child well after the developmental stage at which the secondary flexor movement drops out. It is also in order to ask what possible value the general extension of the upper extremities, often accompanied by tremor, extension of the trunk and throwing back of the head, may have as a preliminary to clasping. The delay between the two phases and the "leisurely" course of the whole response also argue against its adaptive value as a protective reaction. The final argument against Moro's interpretation, however, comes from closer examination of the real nature of this so-called clasping behavior. We have recently made a slow motion analysis of the reflex in a group of infants of various ages. In younger infants the primary extension is generally followed by flexion, which brings the extremities together in front of the body. This is not often seen after the first month. In older infants the extension is followed by gradual return of the arms to the sides in a normal resting position. Careful examination of our pictures suggests that the clasping movements of the younger infants may also be merely a return to a normal resting position—in this case, the flexion position habitual during the first days of life. Thus, the slow flexor movement may be a gradual flexion asserting itself over the extension and returning the arms to their normal flexed position before the chest. The illusion of "clasping" behavior is also furthered by the complications introduced in many younger infants by tonic neck reflexes. Thus, if the infant's head is turned to one side when the Moro reflex appears there is frequently

a righting response in which one arm is thrown out and over as the child attempts to turn the body in alinement with the head. While this looks at first like clasping, it seems best to discard Moro's inter-



The picture (*1*), at the top of each series, shows the infant before stimulation. The succeeding pictures (*2, 3, 4, 5* and *6*) show the development of the response after stimulation (a slap on the bed). Series *A* and *C* show the Moro reflex in older infants; series *B* and *D*, in younger infants.

pretation of the reflex as a clasping response on the grounds that the behavior is better explained as the imposition on the original extension pattern of subsequent postural responses. The accompanying plate

illustrates this. The pictures are to be read from top to bottom. The picture (*1*), at the top of each series, shows the infant before the stimulus (a slap on the bed). The following pictures (*2, 3, 4, 5* and *6*) show the course of the subsequent behavior. Series *A* and *C* show the Moro reflex in older infants, with no secondary flexor movements. Series *B* and *D* show younger babies with the flexor movements complicated by righting responses, giving the appearance of clasping. Whether or not one accepts this explanation, the "clasping" interpretation given by Moro seems erroneous.[9]

The primary response of abduction and extension of the upper limbs, sometimes accompanied by tremor, suggests by its generalized extensor nature a possible similarity to the kind of muscle pattern seen in decerebrate rigidity. Both are reactions which appear if the regulatory cortical influence is diminished.[10] Such a lack of cortical impulses can be concluded from the whole behavior of the baby. It is confirmed by the anatomic evidence of immaturity in the brain at that time. This agrees with the assumption that the decrease and final disappearance of the reaction parallel the development of holding the head erect and of sitting and standing—phenomena which undoubtedly correspond to the degree of maturation of the cerebral cortex. The Moro reflex is thus a sign of immaturity of certain centers of the brain. While it is a normal reaction at a certain stage of development, it is not a normal physiologic phenomenon, in that it indicates lack of maturity. The development of the reflex, its increase or decrease in intensity and its other attributes can act as an index to the progress of maturation. This character becomes especially clear when one compares it with the other response to sudden, intense stimuli—the startle pattern. The startle pattern is totally different from the Moro reflex not only because of the predominance of flexion movements but because of the normal character of the startle pattern. The Moro reflex is a sign of immaturity.

SUMMARY

Both the Moro reflex and the startle pattern may be called forth in infants by the same stimulus. While the Moro reflex gradually disappears, being usually gone by the fourth month of life, the startle pattern becomes regular and perseveres throughout life. Examination of the Moro reflex shows it to consist of two phases: a primary exten-

9. The authors had the opportunity to compare their films with some of those taken by Dr. Margaret Fries.

10. Goldstein, K.: Das Kleinhirn, in Bethe, A., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 10, p. 222; The Function of the Cerebellum from a Clinical Standpoint, J. Nerv. & Ment. Dis. **83**:1, 1936.

sion of the upper extremities and a subsequent flexion or "clasping" movement. The primary extension is the important part of the response, and the secondary "clasping" movement may represent merely the influence of normal postural habits. It thus seems erroneous to refer to the Moro reflex as an adaptive, protective, clasping response. It is rather a phenomenon representative of cortical immaturity.

Case Reports

ARNOLD-CHIARI MALFORMATION AND ITS OPERATIVE TREATMENT

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The Arnold-Chiari malformation is a downward elongation of the cerebellum and brain stem into the cervical portion of the spinal canal associated with spina bifida. Russell and Donald [1] pointed out that it is a more frequent accompaniment of spina bifida than is usually supposed and suggested that the malformation is the actual cause of the hydrocephalus which may also accompany this condition.

Instead of the Arnold-Chiari malformation being a pathologic curiosity, as the rarity of reports in the literature until now would indicate it to be, the anomaly may present itself as an unexpected clinical problem to be dealt with by the neurosurgeon. For that reason, we describe an operation in a case of this condition, with a discussion of the mechanism of its production and suggestions as to the proper operative treatment.

REVIEW OF LITERATURE

In 1894 Arnold [2] described a newborn human monster with a very large lumbosacral myelomeningocele and gross deformity of the lower extremities and viscera. He pointed out that in this case the cerebellum was pulled down into a tail-like extension, which was attached to the spinal cord in what seemed to be the midcervical region. He suggested that it is likely that in cases of lumbosacral spina bifida similar changes may often be produced in the upper portions of the central nervous system.

In 1907, two of Arnold's pupils, Schwalbe and Gredig,[3] made an exhaustive analysis of developmental anomalies in the cerebellum, brain stem and cervical portion of the spinal cord associated with spina bifida and summarized the literature, which had already become voluminous.

From the Montreal Neurological Institute and the McGill University.

Read before the American Association of Neuropathologists, June 1, 1936.

1. Russell, D., and Donald, C.: The Mechanism of Internal Hydrocephalus in Spina Bifida, Brain **58**:203, 1935.

2. Arnold, J.: Myelocyste, Transposition von Gewebskeimen und Sympodie, Beitr. z. path. Anat. u. z. allg. Path. **16**:1, 1894.

3. Schwalbe, E., and Gredig, M.: Ueber Entwickelungstörungen des Kleinhirns, Hirnstamms und Halsmarks bei Spina bifida, Beitr. z. path. Anat. u. z. allg. Path. **40**:132, 1907.

The words "pathologic" and "physiologic" are used in order to conform to the terminology which is compulsory for publication in the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. We should prefer to use the words "pathological" and "physiological."

The most important contribution was that of Chiari,[4] 1895, who one year after Arnold had reported a large series of cases of the malformation, which he had subdivided into groups according to the degree of downward prolongation of the cerebellum and bulb. It is obvious that Chiari had made his observations independently of Arnold; so the condition was appropriately named the Arnold-Chiari malformation.

Russell and Donald[1] again reviewed the literature and added 10 cases. On examining 10 successive specimens of spina bifida sent to the pathologic laboratory of the London Hospital, they were surprised to find in all some degree of malformation of the cerebellum and medulla oblongata. Since their excellent description of the usual features of this condition makes the information easily available in English, it will not be repeated now; they suggest, however, that suboccipital decompression should be considered as a method of treatment of the hydrocephalus which may accompany spina bifida and pointed out that the only report of a surgical attack on the condition was that of van Houweninge Graftdijk.[5] Apparently, the operation in his case had a fatal outcome.

REPORT OF A CASE

History.—M. M., a woman aged 29, who was admitted to the Montreal Neurological Institute, had had an operation at the age of 3 years for the repair of spina bifida with meningocele. The sac, which was located in the upper dorsal region, had evidently been filled with cerebrospinal fluid. After the operation she was well until the age of 16, when she began to have difficulty in hearing. The loss of hearing advanced slowly and did not become important until the age of 27, two years before admission. For about three years before admission she had noticed dimness of vision in the right eye and occasional double vision on looking to either side. For the same time she had noticed that the right eye seemed to water more than normally, and her friends told her there was weakness of the right side of the face. She said that she had lost her position as bookkeeper because tears that she could not wink away fell on her work. For about one year before admission she had had a tendency to fall forward.

Physical Examination.—The patient was normally developed, alert and cooperative. There was a small lump over the upper dorsal portion of the spine, about 3 cm. in diameter, with a linear scar in the overlying skin—the mark of the operation in infancy (fig. 1). General physical examination otherwise revealed nothing abnormal. Neurologic examination revealed the defects to be described. The optic disks were normal except for pallor of the temporal halves and some enlargement of the physiologic cups. Extraocular movements were characterized by nystagmus of a wide range on gaze to the right. On gaze to the left the quick phase of nystagmus was upward and to the left. Upward gaze was somewhat limited and associated with nystagmus, the quick phase of which was upward, the two eyes being affected equally. On looking to the right the left eye lagged, and on looking to the left the right eye moved over incompletely, suggesting bilateral weakness of the oculomotor nerve. The corneal reflex was absent on the right. Tactile sensation was normal over the face. There was definite weak-

4. Chiari, H.: Ueber Veränderungen des Kleinhirns, des Pons und der Medulla oblongata in folge von congenitaler Hydrocephalie des Grosshirns, Denkschr. d. k. Akad. d. Wissensch. Math-naturw. Klasse **63**:71, 1895.

5. van Houweninge Graftdijk, C. J.: Over hydrocephalus, Leyden, Netherlands, Eduard Ijdo, 1932.

ness of the right side of the face of peripheral type, i. e., involving the upper and lower portions of the face equally (fig. 2). Closure of the left eye also was definitely weak. There was bilateral deafness without increase in bone conduction or other evidence of lesion of the middle ear.

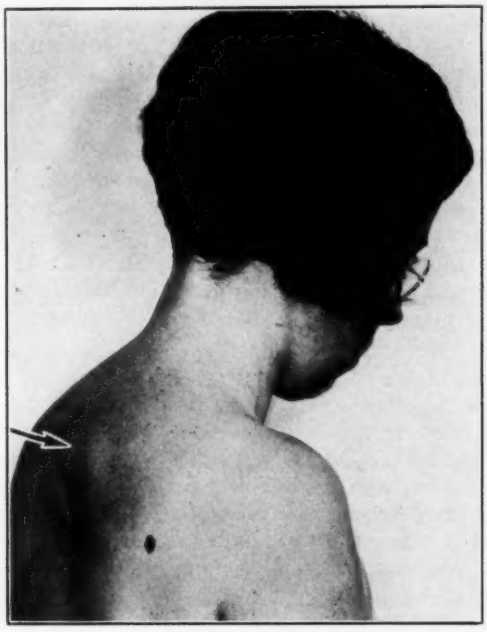

Fig. 1.—Patient just before operation. The arrow indicates the site of operation for spina bifida at the age of 2 years.

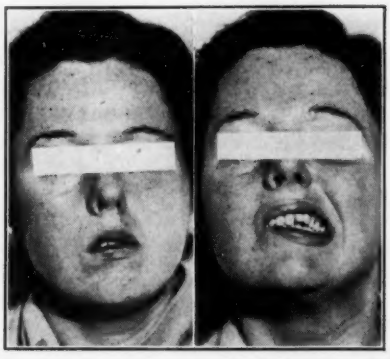

Fig. 2.—Patient with the face at rest (left) and showing the teeth (right). Weakness of the right facial nerve was almost complete, and that of the left was partial.

There was well marked truncal ataxia. The deep reflexes were present, but symmetrically decreased. The plantar responses were normal on the left side and atypical on the right.

Summary.—The important features were as follows: amputation for thoracic spina bifida in infancy; gradually increasing paresis of the sixth, seventh and eighth cranial nerves bilaterally; a recent history of falling forward; truncal ataxia on examination; an unusual type of nystagmus and bilateral paresis of certain cranial nerves.

Diagnosis.—In retrospect it seems that we should have suspected the Arnold-Chiari malformation. Instead, a suboccipital craniotomy was carried out, with a tentative diagnosis of tumor of the acoustic nerve bilaterally.

Operation.—On Nov. 19, 1935, a myoplastic suboccipital craniotomy was done with the patient under avertin and ether anesthesia. The following notes are taken from the report of operation.

"Objective Findings: The transverse sinus was 1 or 2 cm. lower than usual in relation to the external occipital protuberance. An unusual sinus ran in the dura from the lateral sinus down over the cerebellum on the right side. When the dura was opened, a large space was seen between the upper surface of the cerebellum and the under surface of the tentorium.

"Most of the accumulation of spinal fluid which one would expect to see in the cisterna magna seemed here to be above the cerebellum. There was no fluid in the cisterna magna; in fact, after the laminal arches of the cervical vertebrae had been removed, it was seen that the cerebellum passed downward from the posterior fossa, becoming progressively thinner until it ended in a tail beneath the laminal arch of the third cervical vertebra, where it was densely adherent to the pia-arachnoid of the spinal cord (fig. 3 *A*). There were no adhesions between the dura and the arachnoid; between the arachnoid and the pia, however, there were dense adhesions, and the cerebellum was wrapped partially about the cord. A little higher the bulb was also partly surrounded by the cerebellum.

"The medulla oblongata (fig. 3 *B*) was also pulled downward into the spinal canal and, with the spinal cord, was flattened and concave, due to the imprint of the tail of the cerebellum. After the cerebellum had been dissected free, it retracted, owing to its tensible elasticity, and the tip withdrew about 3 cm. from its attachment beneath the third cervical arch. This demonstrates that there had been active, continuous downward traction.

"The brain stem was pulled down so far that the seventh and eighth cranial nerves emerged from the medulla at the level of the foramen magnum. On the left side these nerves were measured from the medulla to the internal auditory meatus. They had been stretched to a length of 5 cm. The ninth and tenth nerves were also long; although they were not measured, it is thought that they were a little longer than the seventh and eighth nerves. The same condition obtained in the angle on the opposite side. There were no adhesions in the angle. The bone over the upper part of the posterior fossa was thick; it became suddenly thin just before reaching the foramen magnum, and the foramen was larger than usual.

"Operative Procedure: An arching incision was made and the whole occipital muscle mass reflected downward. The occipital bone and the arches of the first, second and third cervical spines were removed. The dura was opened, and the cerebellum was dissected free, reflected upward and gently freed from the spinal cord (fig. 3 *A* and *B*). The seventh and eighth cranial nerves were partly caught in this malformation, but were easily freed. The lower end of the tail of the malformation was excised for histologic study. The dura was then closed loosely and the muscle mass fastened to the skull by steel ligatures through drill holes in the bone; the galea and skin were closed in layers."

Course.—At the close of the operation the patient's condition seemed excellent, but, to our surprise, she never regained consciousness, continuing as though in a deep sleep until she died, two months later. During this time she moved all extremities, but had a tendency to respiratory embarrassment, due to bulbar palsy. The cause of death will be discussed later. Permission for postmortem examination was limited to opening the operative wound.

Autopsy.—The dura at the level of the fourth thoracic spine was adherent dorsally to the soft tissues, into which it and the underlying cord were pulled like the peak of a tent (fig. 4). Removal of the brain and cord down to the fifth thoracic segment, including all the nerve roots, was carried out.

The inner table of the skull showed increased convolutional marking, and the sella turcica was depressed. The convolutions of the brain were somewhat flat-

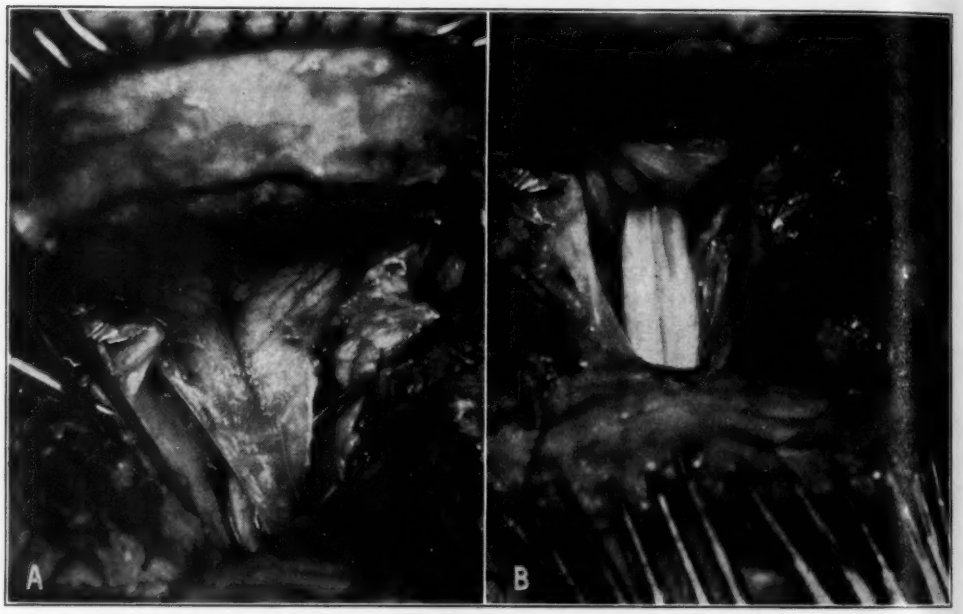

Fig. 3.—Photographs of suboccipital craniotomy. *A*, an instrument has been placed under the elongated tail of the cerebellum, which is still attached by its tip to the leptomeninges of the cervical portion of the cord. *B*, the cerebellar tail has been turned back and the brain stem exposed. The cranial nerves can be seen on the right passing upward into the posterior fossa.

tened; the cortex was thin, particularly on the ventral surface of the temporal lobes, and old pigment was scattered over the leptomeninges. There was extreme dilatation of the lateral and third ventricles, as shown in figure 4. The middle and anterior commissures were flattened, as well as the corpus callosum. A notch on the posterior aspect of the cerebellum indicated the point at which it had pressed on the edge of the foramen magnum, owing to its downward pull.

The brain stem was markedly elongated and narrowed and measured 8.5 cm. from the incisural notch of the tentorium to the inferior angle of the fourth ventricle in the spinal canal (fig. 4). There was a depression in the medulla oblongata, approximately 1 mm. in depth and 1 cm. in diameter, at the point

where it had impinged on the ventral edge of the foramen magnum. This area appeared pale on removal, as though it had been compressed. The vessels at the base, particularly the basilar artery, which had grooved the ventral surface of the brain stem were tightly stretched.

Most of the cranial nerves were markedly elongated (fig. 5). After the brain had been removed, the measurements from the brain stem to the point of exit

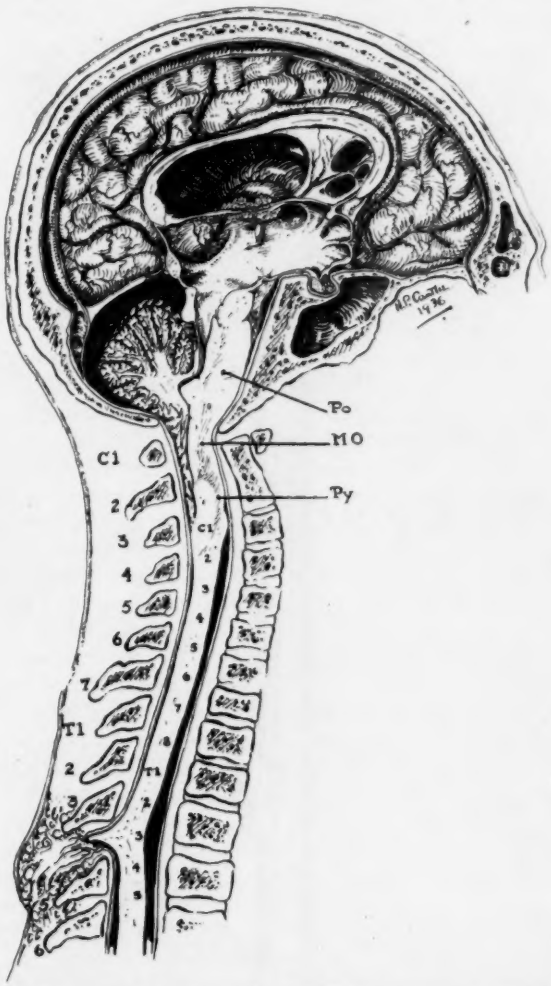

Fig. 4.—Schematic reproduction prepared after autopsy. Note the dilatation of the ventricular system produced by closure of the fourth ventricle due to wedging of the cerebellum and brain stem into the cisterna magna. In this figure and in figure *5, Po* indicates the pons; *M O,* the medulla oblongata, and *Py,* the decussation of the pyramids.

through the dura were as follows: third cranial nerve, 2.4 cm.; fourth, 3.5 cm.; fifth, 2.5 cm.; sixth, 4.5 cm.; seventh, 4.4 cm.; eighth, 5.1 cm., and ninth and tenth, each, 3.5 cm.

The course of the spinal roots on the left side were as follows (fig. 5): Before they reached the dural exit and ascended, the second, third, fourth and fifth cervical roots ascended, respectively, 3, 1.7, 1.6 and 1.5 cm.; the sixth cervical root ascended slightly; the seventh cervical root ran perpendicularly; the eighth cervical root descended slightly, and the first and second thoracic roots descended 1 and 1.7 cm., respectively. The third and fourth thoracic roots descended 1.6

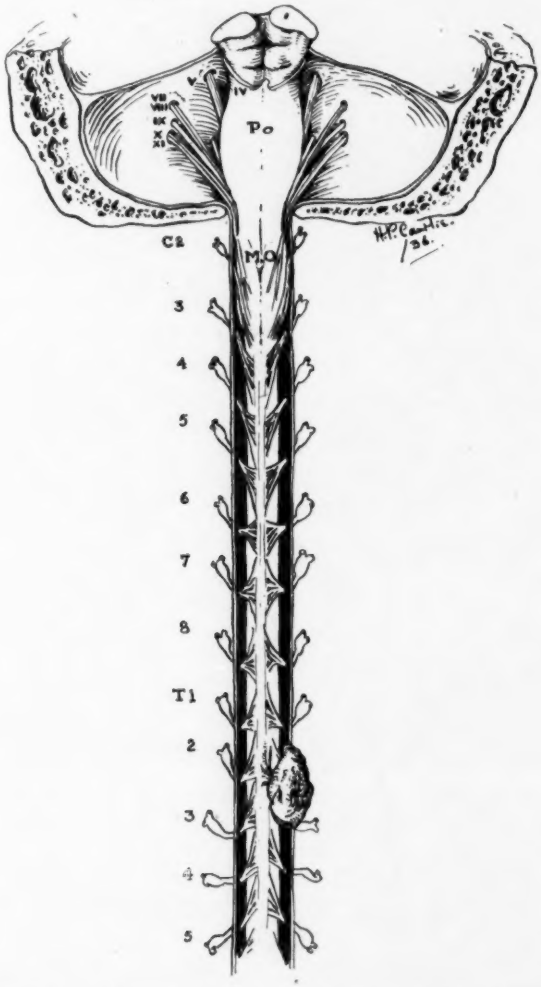

Fig. 5.—Diagram to show the brain stem, cord and myelomeningeal attachment. The cranial and spinal nerves are seen in relation to their passage through the dura.

and 2.5 cm., respectively, to the dural exit and then ran horizontally, and the fifth thoracic root descended 2.8 cm. to the dural exit and then descended slightly.

There were great dilatation of the lateral and third ventricles and communication of the third ventricle with a dilated space above the pineal gland. The general

dilatation included the first third of the aqueduct of Sylvius (fig. 4). Below this point the aqueduct was narrow, and the fourth ventricle was functionally closed by protrusion upward of a triangular tongue of brain stem, as shown in figure. 4.

The brain stem was enormously elongated and was flattened and thinned from before backward, the spinal cord being also flattened. The pons measured 1.5 cm. dorsoventrally; the medulla, 1.2 cm. at its thickest point, and the cord, 0.65 cm. at the fifth cervical and first thoracic segments. The length of the pons was 4 cm. and that of the medulla, 3.2 cm. The attachment of the spinal cord at the third thoracic segment was made up of grayish white scar tissue, which extended dorsally into scarred muscle and fatty tissue.

SUMMARY AND COMMENT

The primary elements in this abnormality were attachment of the spinal cord and dura to the bifidal protrusion, moderate congenital smallness of the cerebral convolutions and, possibly, proportional smallness of the cerebellum. The other abnormal conditions were evidently produced by the mechanical traction exerted at the site of the spina bifida as a result, first, of growth and, later, of cicatricial contraction.

The brain stem was elongated. The pons was long and slender, but the top of the bulb was the thinnest portion of the brain stem. The posterior portion of the pons composing the floor of the fourth ventricle was squeezed upward to fill the space of the fourth ventricle. The whole of the bulb, that is, the medulla oblongata, was outside the cranial cavity. There was a slight depression in the anterior surface of the bulb resulting from pressure of the bone at the level of exit of the seventh and eighth cranial nerves and also at the formation of the basilar artery. This point of pressure may have been important in the production of paralysis of the seventh and eighth nerves.

The cranial nerves, especially the seventh, eighth, ninth and tenth, were thin and elongated.

Traction was exerted on both the spinal cord and the dura by the myelomeningeal attachment at the fourth thoracic segment. Traction on the cord was indicated by the elongation of the brain stem and the increased length and upward course of the thoracic spinal nerves outside the dura when the corresponding intradural roots descended to their dural exit. Traction was exerted downward on the cerebellum by means of its attachment to the leptomeninges of the spinal cord, as shown by its elongated shape, the space between the upper surface of the cerebellum and the under surface of the tentorium and the fact that the cerebellum retracted after being dissected free at operation.

Internal hydrocephalus resulted from functional internal block in the fourth ventricle due to molded pressure which surrounded it. It is probable that both the aqueduct and the ventricle were capable of allowing fluid to pass when the pressure above rose high enough. There was no evidence of a block at the base.

During normal growth the dura elongates with the increasing length of the trunk. The spinal cord also grows in length, but proportionally less than the trunk. The brain stem, within the cranial cavity, therefore, anchors the whole cerebrospinal axis under normal conditions, and the sacral end of the spinal canal moves away from the cord with the growth of the trunk. Thus, the spinal roots are caused to elongate, the lower most and the higher least.

In this case, however, the myelomeningocele at the level of the fourth thoracic segment formed the fixed point which anchored the spinal cord. During growth the cranial cavity grew away from it, causing greater stretching of the brain stem and cranial nerves than of the spinal nerves (fig. 5). Nevertheless, satisfactory adjustment and elongation of structures took place, and the patient grew to adult life without untoward symptoms and was able to earn her own living.

Gradually, however, in adult life cicatricial contraction occurred at the site of the myelomeningocele, on which operation had been performed in infancy without separation of the cord from the protrusion. That this contraction occurred is indicated by the downward displacement of the thoracic nerves at the point of their passage through the dura (fig. 5). This cicatricial contraction also acted on the cord, increasing the already existent traction on the cerebellum and brain stem and thus wedging them farther down into the foramen magnum. This may have produced enlargement of the foramen. The wedging prevented proper circulation of cerebrospinal fluid and produced the internal hydrocephalus. The hydrocephalus added an element of pressure from above, increasing the pressure on the medulla and producing the gradually increasing paresis of the cranial nerves.

Effect of Operation.—Relief from traction on the cerebellum by cutting it away from its attachment probably exposed the bulb to a still greater pull, as it was then subjected to all the traction, part of which had previously been taken up by the cerebellum. This change may well have shut off the flow of blood through the basilar artery at the point of its angulation over the edge of the foramen magnum. The operation relieved the hydrocephalus, as proved by study of the cerebrospinal circulation before the patient died. This, however, was not enough.

Future Operative Advice.—The following steps should be carried out in case such an abnormality is disclosed at operation: 1. The cerebellar tongue is left attached and the arachnoid opened on either side; the cisterna magna is decompressed by removing its posterior wall and the first and second cervical spinal laminal arches. These two steps will be adequate to relieve the hydrocephalus. 2. The spina bifida is exposed, and the dura cut free about it and the attachment to the cord is freed. This will relieve the cicatricial traction. If possible, the two operations should be done simultaneously.

This case serves to emphasize the necessity for proper initial operation on myelomeningocele with spina bifida, even when it seems to be without complication. If the neural tissue had been dissected free when the patient was 2 years of age and left under a fascial tent, as described by Penfield and Cone,[6] the cicatricial adhesion would probably never have formed.

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6. Penfield, W., and Cone, W.: Spina Bifida and Cranium Bifidum, J. A. M. A. **98**:454 (Feb. 6) 1932.

DISTRIBUTION OF AFFECTED NERVE CELLS IN A CASE OF AMYOTONIA CONGENITA

J. LeRoy Conel, Ph.D., Boston

The general appearance of affected cells in cases of amyotonia congenita and Werdnig-Hoffmann disease has been described by Marburg,[1] Foot,[2] Grinker[3] and others. An autopsy performed at the Children's Hospital in a case of this rare disease has made possible a study of all parts of the brain and spinal cord.

CLINICAL REPORT OF CASE

Case 1.—*History.*—A boy, born on July 14, 1934, was admitted to the Infants' Hospital on November 13 because of weakness. The family history was of interest in that there had been nine pregnancies. The second and third pregnancies terminated in the birth of children who lived eleven and nine months, respectively, and died of muscular weakness and pneumonia. The sixth, seventh and eighth pregnancies terminated in miscarriages. The patient was born normally at full term. There were no evident postnatal complications. The child progressed well after birth except for frequent colds and progressive muscular weakness. During the second week immediately preceding admission to the hospital, he scarcely moved his legs.

Examination.—The patient was bright, happy and well nourished. There was an abundance of firm subcutaneous tissue, which seemed flabby over the upper extremities. The ocular fundi were normal. The musculature was markedly hypotonic. Physical examination otherwise revealed essentially normal structures. The heart, lungs and abdomen showed nothing unusual. The deep reflexes could not be elicited. Stimulation with a galvanic current yielded no contraction. Roentgenograms of the lungs were essentially normal; those of the extremities showed that the long bones were pale and deficiently calcified. The muscular structures appeared underdeveloped.

This investigation has been assisted by grants from the William W. Wellington Memorial Research Fund and the Rockefeller Foundation.

From the Department of Anatomy, the Boston University School of Medicine and the Massachusetts Memorial Hospitals, and the Departments of Pathology of the Harvard University Medical School and the Children's Hospital.

1. Marburg, O.: Zur Klinik und Pathologie der Myatonia congenita (Oppenheim), Arb. a. d. neurol. Inst. a. d. Wien. Univ. **19**:133, 1911; Zur Pathologie der Myatonia congenita, Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. **10**:194, 1911.

2. Foot, N. C.: Report of a Case of Amyotonia Congenita (Myatonia Congenita Oppenheim) with Autopsy, Am. J. Dis. Child. **5**:359 (May) 1913.

3. Grinker, R. R.: The Pathology of Amyotonia Congenita: A Discussion of Its Relation to Infantile Progressive Muscular Atrophy, Arch. Neurol. & Psychiat. **18**:982 (Dec.) 1927.

The infant followed objects with the eyes and was much interested in what was going on about him. He seemed to breathe entirely with the abdomen. He could not lift the head, but turned it from side to side; he moved the arms easily, but did not take hold of objects well. The cry was strong and loud. There was no difficulty in eating.

Course.—On the day before death the infant seemed much the same, except that respirations were a little noisy and breathing was becoming more difficult; however, he still ate well and appeared happy; there was no evidence of infection. On the morning of November 21 he was discovered to be practically moribund; he was cyanotic and had vomited recently. Artificial stimulation, with oxygen, carbon dioxide, etc., failed to produce any lasting effects.

Tests for Muscle Efficiency.—These tests were made by Miss Janet B. Merrill, director of physical therapeutics at the Children's Hospital. The results of the tests were as follows: The infant could not sit alone; he did not kick with the legs when angry because the extensor muscles were very weak. There were slight flexor-abductor contraction of the hip joint and slight flexor contraction of the knee joint. When he was held in a sitting position he could balance the head and turn it from side to side; he could not raise the head while lying in either the prone or the supine position. The sacrospinalis, abdominal and gluteus maximus muscles were in poor condition. The action of the flexor and abductor muscles was fair, but that of the adductor muscles was poor. Stimulation of the quadriceps femoris muscle produced only a trace of movement. Contraction of the hamstring and gastrocnemius muscles was fair. The other muscles of the leg were in good condition. Contraction of the anterior part of the deltoid muscle was fair, but that of the posterior part was poor. The upper part of the trapezius muscle responded well, and the middle and lower parts fairly well. Contraction of the serratus magnus, rhomboideus major and minor, latissimus dorsi, pectoralis major and outward rotator muscles was fair. The biceps muscle reacted well. The triceps and supinator radii brevis muscles were fair. Contraction of the pronator, flexor carpi radialis and ulnaris, extensor carpi radialis and ulnaris and flexor digitorum profundus and sublimis muscles was good. Response of the extensor muscles of the fingers was fair. The lumbricalis, interosseus dorsalis and volaris, abductor digiti quinti, opponens digiti quinti, abductor pollicis and flexor and extensor muscles of the thumb contracted well.

REPORT OF AUTOPSY

Material and Methods.—The entire brain and spinal cord and some of the sympathetic trunk were removed; unfortunately, no dorsal root ganglia were saved. The brain and spinal cord were hardened *in toto* in a dilute-solution of neutral formaldehyde U. S. P. (1:10). Small blocks of tissue were cut from the lumbosacral, thoracic and cervical regions of the spinal cord, and sections were prepared by the Cajal, Golgi-Cox, Weigert, hematoxylin and eosin and cresyl violet methods; serial sections were cut for staining with hematoxylin and eosin. Serial sections were made through the brain stem in the region of each cranial nerve, from the third to the twelfth, and were stained with hematoxylin and eosin. One small block of the brain stem through the inferior olive and another through the pons were prepared by the Weigert method. Pieces of the sympathetic trunk were fixed in Zenker's fluid, cut in serial sections and stained with hematoxylin and eosin.

Sections through various parts of the thalamus and corpus striatum were prepared by the Cajal, Golgi-Cox, Weigert, hematoxylin and eosin and cresyl violet methods. Each of these methods was used also in preparing sections from

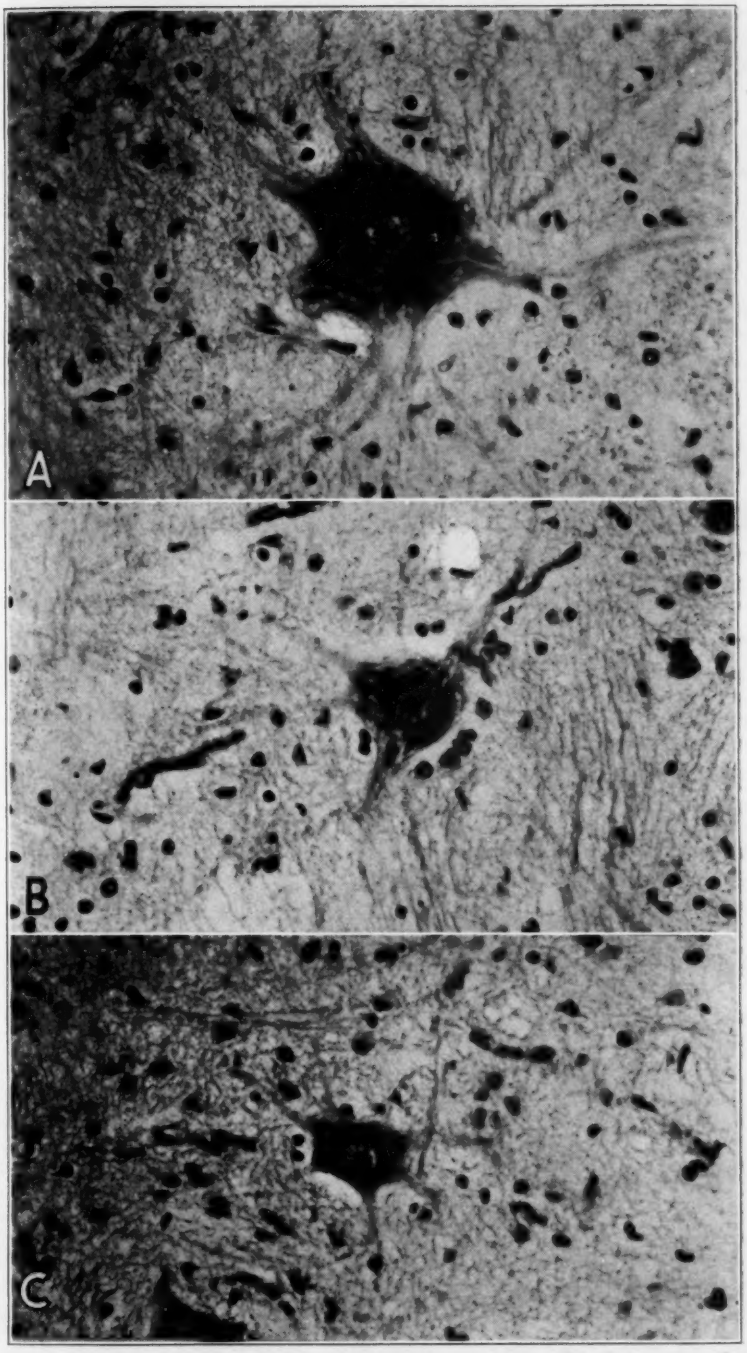

Fig 1.—Typical normal somatic efferent cells in the ventral column of the gray substance of the spinal cord. Hematoxylin and eosin stain; × 370. *A* is a giant cell; *B*, a medium-sized cell, and *C*, a small cell.

The photomicrographs in this figure and in the accompanying figures were made by Mr. Charles Miller.

five regions of the cerebellum, including the nuclei, and from thirty-five regions of the cerebral cortex; serial sections through each of the functional regions of the anterior and posterior central gyri were stained with hematoxylin and eosin.

For the purpose of comparison, serial sections were cut through the various regions of the spinal cord of 3 other infants of approximately the same age. The first infant (control case 2), 5 months old, had a condition diagnosed as intussusception; the second (control case 3), 4 months old, had meningitis, and the third (control case 4), 4 months old, a congenital defect of the kidney.

Observations.—Nervous System: In the normal somatic efferent cell (fig. 1) of the ventral column of the gray matter, the nucleus was approximately central in position; the chromaffin particles were scattered irregularly throughout the nucleus, and the Nissl bodies were large and coarse and were distributed uniformly throughout the cell body and in the dendrites. The cytoplasm stained very light pink with hematoxylin and eosin and not at all with cresyl violet.

The appearance of the affected cells suggested a gradual progression of changes, as follows: In the earliest stages of involvement the cytoplasm stained deep pink with hematoxylin and eosin and purple with cresyl violet; the nucleus had moved slightly from its central position and was usually enlarged; the Nissl bodies nearest the center of the cell had moved away from the center and had broken down into smaller particles (fig. 2*A*). The nucleus and Nissl bodies had moved progressively farther from the center of the cell; more of the Nissl bodies were crumbled, and the cell body usually, though not always, was increased in size (fig. 2*B*). The nucleus and Nissl bodies were finally crowded against the cell wall; the tigroid bodies were much reduced in size and number, although a few large masses remained; the chromaffin material in the nucleus was reduced in quantity, but the nucleolus and nuclear wall remained; large Nissl bodies were still present in the dendrites, and the cell body was usually swollen (fig. 2*C*). Cajal silver preparations disclosed that the neurofibrils were intact but were crowded against the cell wall. Later, the nucleus was flattened against the cell wall or crowded into a dendrite; the chromaffin material was further reduced in quantity; only a few small Nissl bodies were left crowded against the cell wall, either singly or in clumps, and the size and number in the dendrites were much reduced; the cytoplasm had a homogeneous colloid appearance; a small clump of granules appeared near the center of the cytoplasm (fig. 2*D*). The granules became more numerous; the cytoplasm immediately surrounding the clump stained more lightly than the rest, and the Nissl bodies were further reduced in size and quantity (fig. 2*E* and *F*). The clump of granules and the surrounding light area in the cytoplasm continued to enlarge, approaching the cell walls; the Nissl bodies were further reduced in size and quantity, and the nucleus diminished in size and began to disintegrate (fig. 3*A*). Finally, all the cytoplasm stained light, and only traces of Nissl substance and the nucleus were left, flattened against the cell wall (fig. 3*B*). Throughout the course of these changes the cytoplasm presented a hyaline appearance and stained light purple in the pale circle and deeper purple beyond the periphery of this area. The granules in the center also stained light purple. Eventually, no Nissl substance remained, either in the cell body or in the dendrites. The cytoplasm now began to shrink and stained much deeper purple (fig. 3*C*). The cytoplasm continued to shrink and collected at the center in a mass from which radiating strands were directed peripherally. Small cells, probably glia cells, gathered around the periphery (fig. 3*D*). The cytoplasm continued to shrink, stained increasingly faintly and finally disappeared, leaving only a light space which contained a few fibrous strands and was surrounded by nerve fibers; the small cells remained around

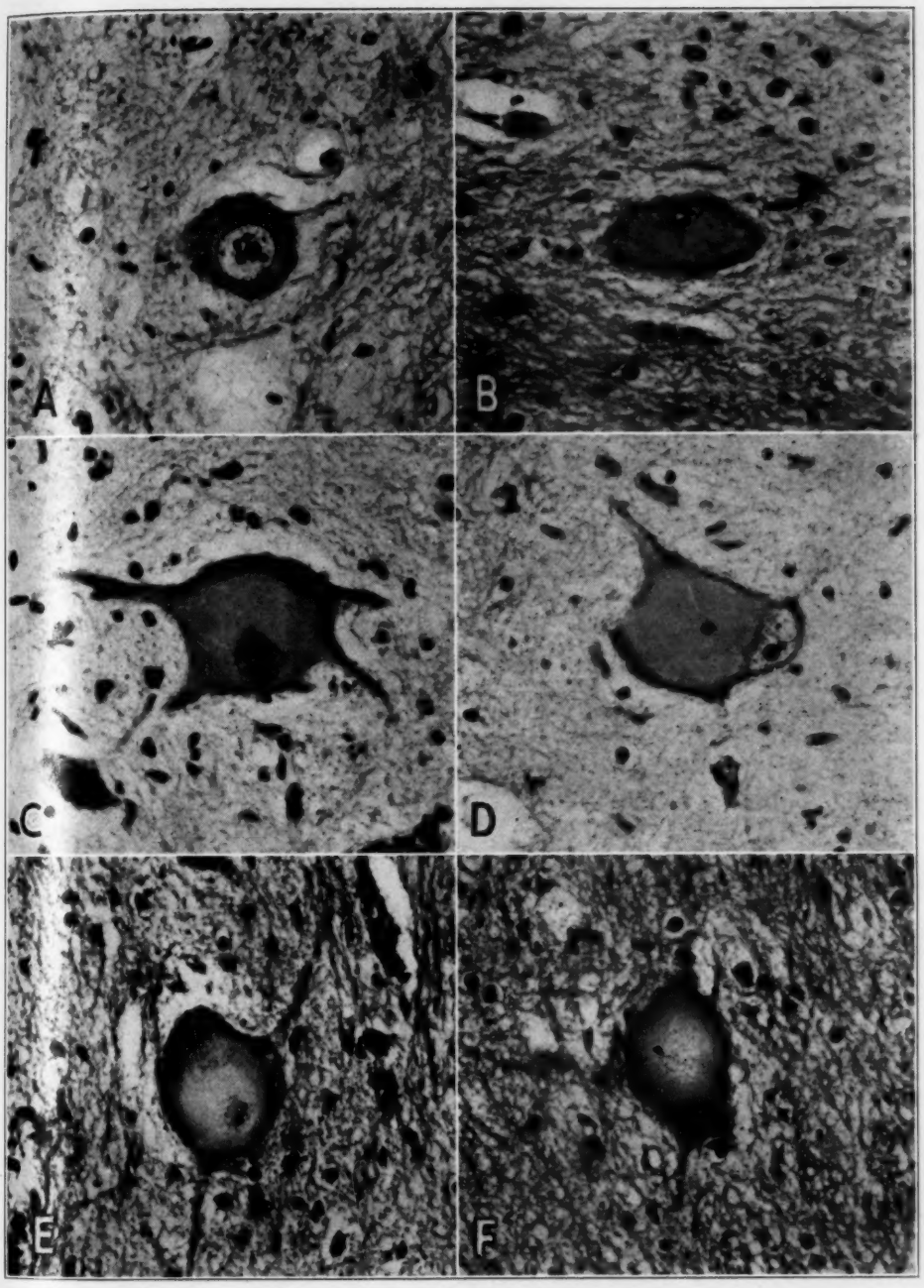

Fig. 2 (case 1).—Photomicrographs (hematoxylin and eosin; × 370) arranged in consecutive order to illustrate the progressive changes which occur in an affected nerve cell in amyotonia congenita. *A* shows the earliest stage of involvement, in a cell in the thoracic region of the spinal cord; *B*, a slightly later stage, in a cell in the cervical enlargement of the cord; *C*, a stage slightly later than that shown in *B*, in a cell in the lumbar region of the cord; *D*, a stage later than that shown in *C*, in a cell in the upper cervical region; *E*, a stage later than that shown in *D*, in a cell in the cervical enlargement, and *F*, a stage later than that shown in *E*, in a cell in the cervical enlargement of the cord.

the nerve cell until it had completely disappeared (figs. 3 *E* and *F* and 4 *A*). The nucleus withstood these changes longer than the Nissl bodies, and the nucleoli remained longer than any other part of the nucleus. Cajal preparations showed that the neurofibrils outlasted the Nissl substance and that they remained in the processes for a longer time than in the cell body.

For purposes of reference, these continuous and progressive changes may arbitrarily be divided into three stages: (1) an early stage, which may be said to end when the nucleus and the Nissl bodies are crowded against the cell wall (fig. 2 *A, B* and *C*); (2) an intermediate stage, which begins with the appearance of the clump of granules and the light circle in the cytoplasm (figs. 2 *D, E* and *F* and 3 *A* and *B*), and (3) the late stage, which begins with the shrinking of the affected cell (fig. 3 *C* to *F*).

In 244 serial sections, each 8 microns thick, of the lumbar enlargement of the spinal cord, representing a piece 1.95 mm. long, there were counted 100 affected cells, all of which were located in the ventral columns of the gray matter. Of these affected cells, 46 were in the left ventral column and 54 in the right; 70 were in the early and intermediate stages of involvement, and 30 were in the late stages. A few spaces left by atrophied cells were present in each ventral column. The normal cells were distributed longitudinally in small aggregations, separated by intervals in which there were few or no cells. In a section which passed through such an aggregation, from 10 to 20 normal cells could be counted in each ventral horn.

In 244 serial sections, each 8 microns thick, through the thoracic region of the cord, 22 affected cells were counted in the ventral columns of the gray substance, 14 of which were in the right column and 8 in the left. Of the affected cells, 12 were in the early and intermediate stages and 10 in the late stages. Spaces left by atrophied cells were seen much more frequently here than in the sections of the lumbar enlargement. In the thoracic region also the normal cells were distributed longitudinally in aggregations. No more than 4 normal cells were counted in either ventral horn in any one section of this region, and in many sections no normal cells were present. As compared with the observations in control cases 2 and 4 from 8 to 15 cells were present in each ventral horn in a section which passed through an aggregation of cells in the thoracic region of the cord, and in few sections were cells entirely lacking in either ventral horn. The thoracic region of the cord in case 1 showed a considerably greater degree of involvement than the lumbar enlargement. Spaces left by atrophied cells were more numerous, and there was a greater proportion of affected cells in the late stage than in the lumbar enlargement.

In 144 serial sections, each 8 microns thick, from the cervical enlargement of the cord, representing a piece 1.15 mm. long, 77 affected cells were counted, 36 of which were in the right and 41 in the left ventral column of the gray matter. Of the affected cells, 47 were in the early and intermediate stages and 30 in the late stages. Spaces left by atrophied cells were less numerous than in either the thoracic or the lumbar region. In a section which passed through an aggregation of cells, the normal large cells in either ventral horn numbered from 6 to 12, and the normal small cells, from 15 to 20. The large cells were almost entirely confined to the lateral part of the ventral column, that is, in the location of cells which send their axons to the muscles of the upper extremity, while the small cells occurred only in the medial part of the column, i. e., in the region of cells supplying fibers to the trunk muscles; a large cell was seldom seen in the medial part of the ventral column in this case. There were more normal cells in proportion to the affected cells in the cervical than in the lumbar enlargement.

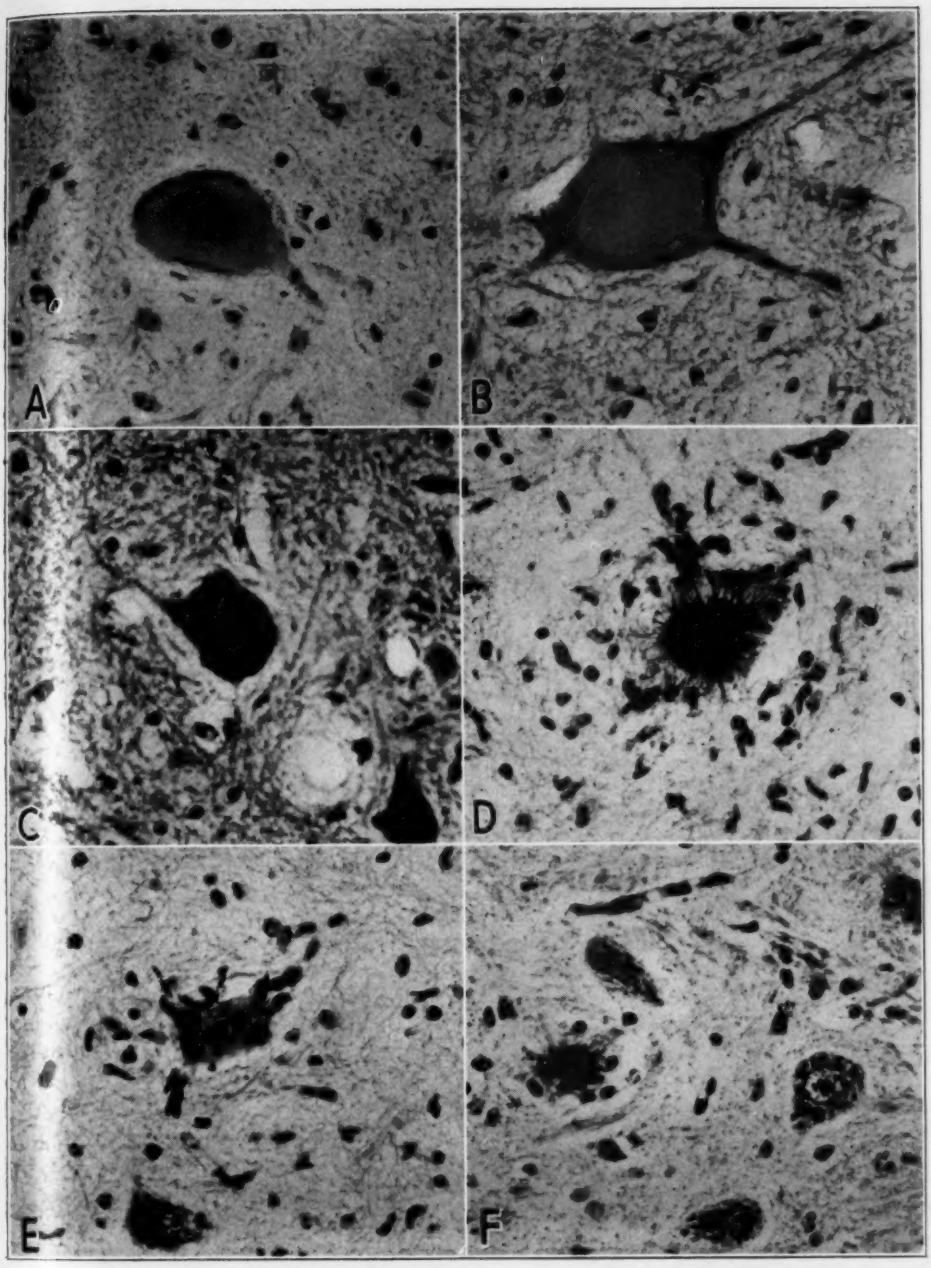

Fig. 3 (case 1).—Photomicrographs (hematoxylin and eosin; × 370) arranged consecutively, showing stages later than those illustrated in figure 2. *A* represents a stage later than that shown in figure 2*F*, in a cell in the nucleus of the hypoglossal nerve. There are Nissl bodies at the margin of the cell and in the dendrites only and an enlarging clump of granules in the cytoplasm. *B* is a stage later than that shown in *A*, in a cell in the thoracic region of the cord, and *C*, a stage later than that shown in *B*, in a cell in the thoracic region of the cord. The Nissl substance is entirely gone. The cytoplasm is shrinking and stains deep purple. *D* is a stage later than that shown in *C*, in a cell in the lumbar region of the cord. The cytoplasm stains deep purple and is collected at the center of the cell, with strands radiating outward. Small cells are gathered around the periphery of the cell. *E* is a stage later than that shown in *D*, in a cell in the lumbar region of the cord. The cytoplasm is disappearing and stains lightly; small cells are still gathered around the remains of the nerve cell. A normal cell is shown in the field. *F* is a stage later than that in *E*, in an atrophying cell in the nucleus of the facial nerve. Four normal cells are in the field.

In control case 3, in each section passing through an aggregation of cells in the cervical region of the cord there were from 10 to 14 large cells in the lateral part of the ventral column and from 6 to 10 large cells and from 10 to 15 small cells in the medial part.

In 144 serial sections, each 8 microns thick, of the upper cervical region of the spinal cord in case 1, there were 45 affected cells, 19 of which were in the right ventral column and 26 in the left; only 5 of the affected cells were in the late stage. Spaces left by atrophied cells occurred approximately in the same proportion as those in the cervical enlargement. In the upper cervical region the cells in the ventral column were distributed longitudinally more uniformly than in regions below this level. From 1 to 6 normal cells were present in each ventral horn in each section; the proportion of normal to affected cells and spaces left by atrophied cells was about the same as that in the thoracic region.

The ventral column of gray substance could be traced through the regions of the decussations of the pyramids and the medial lemniscus to the nucleus of the hypoglossal nerve. Affected cells were present along the entire extent of this region of the ventral column; occasional affected cells were seen in the lateral part of the gray substance, along which were scattered the branchial (special visceral) efferent cells of the accessory nerve, which supplies the trapezius and sternocleidomastoid muscles. Normal cells outnumbered the affected ones. Affected cells in the late stage and spaces left by atrophied cells occurred in diminished numbers.

In almost every section through the nucleus of the hypoglossal nerve on each side, from 1 to 4 or 5 affected cells were present; most of these were in the early and intermediate stages, with few in the late stages; spaces left by atrophied cells were rarely seen. In every section through the nucleus on each side, from 10 to 30 normal cells could be counted; the number of sound cells in proportion to that of affected cells was far greater than in any region below this level.

An occasional affected cell was seen in the nucleus ambiguus on each side. This is a branchial (special visceral) efferent nucleus, the cells of which send their axons to the muscles of the larynx through the superior and inferior laryngeal branches of the vagus nerve and to the muscles of the pharynx through branches of the vagus and glossopharyngeal nerves. Most of the affected cells were in the early and intermediate stages; rarely was one seen in the late stage, and no spaces left by atrophied cells were observed.

In each section through the central part of either the right or the left nucleus of the facial nerve, from 5 to 8 affected cells and from 45 to 65 normal cells were present. Most of the affected cells were in the early and intermediate stages; cells in the late stage and spaces left by atrophied cells were seen only rarely. Large multipolar cells with coarse Nissl bodies were scattered throughout the medial part of the reticular formation. In the entire extent of the reticular formation only 1 affected cell was observed, which was in the intermediate stage.

No affected cells were present in the branchial (special visceral) efferent nucleus of the trigeminal nerve or in the somatic efferent nuclei of the abducens and trochlear nerves.

The left nucleus only of the oculomotor nerve stained with hematoxylin and eosin and cresyl violet; Golgi-Cox preparations of the right nucleus were made. Approximately 200 normal cells could be counted in each section through the central part of the left oculomotor nucleus. Only 7 affected cells were present in the entire nucleus, and all were in early or intermediate stages (fig. 4*B*).

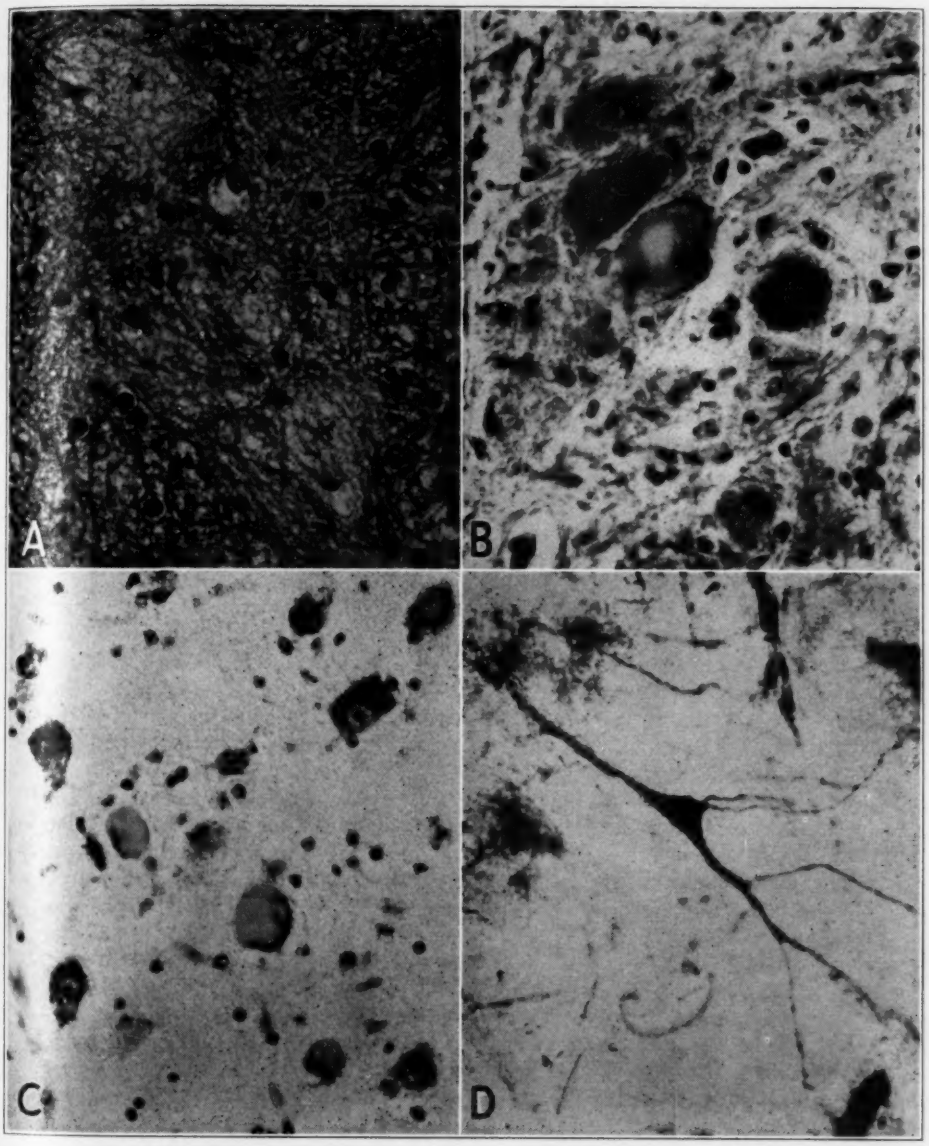

Fig. 4.—*A*, three spaces (*x*) left by atrophied cells in the thoracic region of the spinal cord. Hematoxylin and eosin; × 370. *B*, an affected cell and 3 normal cells in the nucleus of the oculomotor nerve. Hematoxylin and eosin; × 370. *C*, affected and normal cells in the globus pallidus. Hematoxylin and eosin; × 370. *D*, a lanceolate cell in the spinal cord. Golgi-Cox method; × 370.

In one section a group of small cells was arranged in radiating manner around a small space.

In every section through the globus pallidus a few affected cells could be seen; hundreds of normal cells were present in each section (fig. 4 *C*). The cells were multipolar and larger than neighboring cells of the putamen or thalamus and contained large Nissl bodies. No affected cells were observed in the putamen, caudate nucleus or any part of the diencephalon.

Careful search through sections of the thirty-five blocks of the cerebral cortex resulted in the discovery of only 4 affected cells. Each was a giant pyramidal cell of Betz in the anterior central gyrus—1 in the functional area for the trunk, 1 in the area for the lower extremity and 2 in the area for the upper extremity.

Thorough search through sections of the brain, spinal cord and sympathetic trunk disclosed that the involvement of neurons was the only specific and characteristic manifestation of disturbance in the nerve cells caused by this disease. Foot [2] observed many shrunken cells and cells of the "arrow head" type. In every case in which I made examination, cells of the latter type were numerous in the anterior column of the spinal cord, particularly immediately posterior to the large somatic efferent cells. The Golgi-Cox method revealed that these cells had long processes and presented the appearance of normal cells (fig. 4 *D*). They were probably Golgi cells of type II. Shrunken cells were present in all parts of the gray matter of the spinal cord and brain stem and in the thoracic sympathetic ganglia. Whether the shrinking resulted from this disease is problematic; similarly shrunken cells are present in almost every spinal cord and brain stem removed at autopsy. The number of shrunken cells in the gray substance of the spinal cord in case 1 did not seem greater than that in the cords in control cases 2, 3 and 4.

Sections prepared by the silver nitrate method of Cajal revealed that the number of fibers in the ventral rootlets of the spinal nerves of the infant with amyotonia (case 1) was considerably reduced as compared with the number in the corresponding rootlets of the cords of infants of the same age who did not have the disease. Weigert sections revealed only a few myelinated fibers in the ventral roots. Some of the fibers, however, were as well myelinated as those in the ventral rootlets and roots of the spinal nerves of other infants of the same age. Cajal and Weigert preparations disclosed also that the dorsal roots of the spinal nerves of the infant in case 1 were as full of fibers as those of other infants of the same age and that as many were myelinated. There was no evidence of atrophy of fibers or degeneration of myelin in either the dorsal roots of the spinal nerves or the afferent roots of the cranial nerves. Apparently, the afferent limb of the reflex arc in the spinal and cranial nerves was not affected. Transverse sections of the spinal cord of the first infant (case 1) prepared by the Weigert method showed that the fiber tracts presented the same appearance as those in the cords of other children of the same age. The dorsal funiculus was especially prominent in the cords of all infants at the age of 4 or 5 months; at this age the pyramidal tracts stain lightly by the Weigert method. These features become apparent on comparison of *A*, *B* and *C* of figure 5. *A* is a photograph of a Weigert section through the normal spinal cord in control case 2; *B*, a photograph of a section through the cord in case 1, and *C*, an enlarged view of the dorsal and ventral roots of the cord shown in *B*.

Muscles: The report of macroscopic examination of the muscles, made at autopsy by Dr. L. J. McDermott, follows.

"Specimens of the abdominal, pectoral and psoas and both gastrocnemius muscles were removed for chemical and histologic examination. The pectoral and psoas

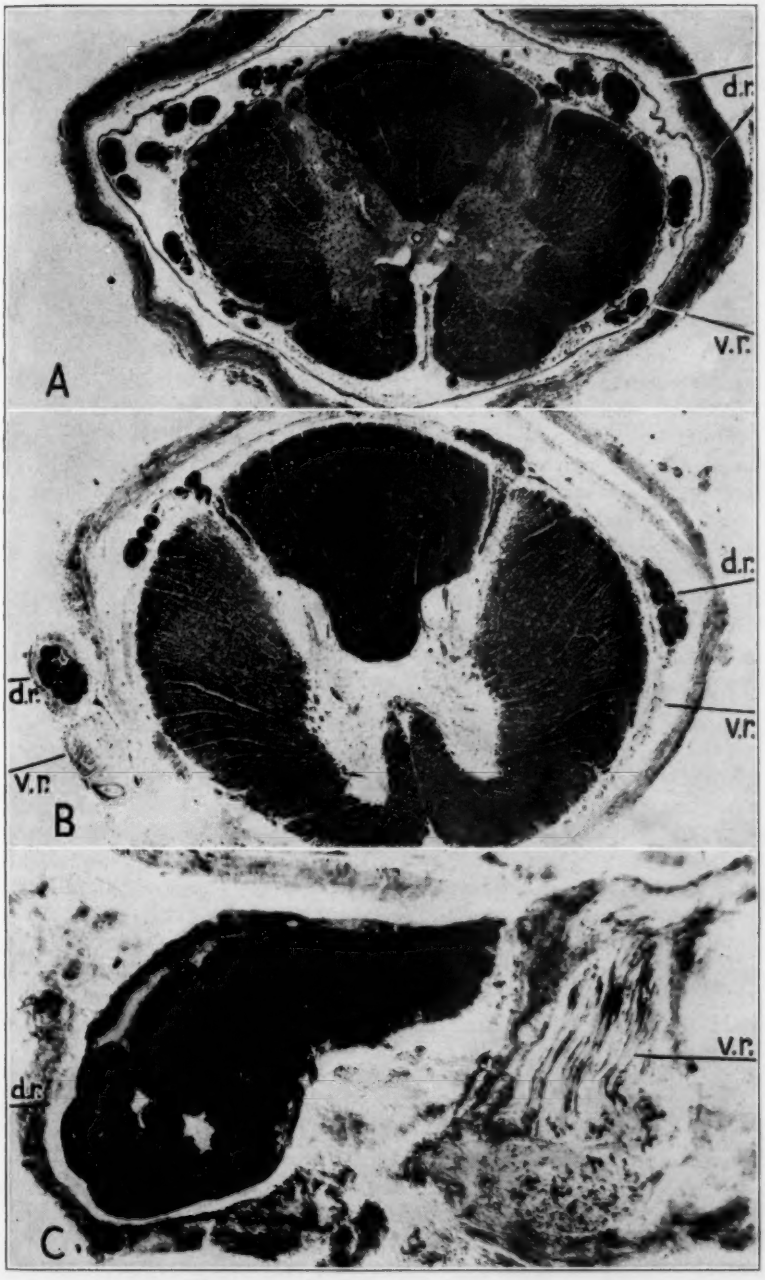

Fig. 5.—Weigert sections through (*A*) a normal spinal cord in control case 2, (*B*) the spinal cord in a case of amyotonia congenita (case 1) and (*C*) the dorsal and ventral roots of the spinal cord in case 1. In this figure *d.r.* indicates the dorsal root, and *v.r.* the ventral root.

muscles were of the usual dark red color and presented no remarkable features on cross section. The abdominal muscles, however, appeared somewhat paler than usual, but no evidences of unusual gross changes were noted. Sections of the diaphragm were dark reddish brown and showed no evidence of inflammatory change or fibrosis. Both gastrocnemius muscles, however, were soft and pale, being strikingly grayish pink. Cross sections of these muscles, however, failed to show any gross evidences of fibrosis or degenerative change."

The report of microscopic examination of the striated muscle, made by Dr. Orville T. Bailey, follows. "The muscles taken from various locations presented the same general picture. The muscle fibers in each location, however, varied considerably in appearance. Some of the fibers were large, with sarcolemmal nuclei at some distance from one another. These fibers stained lightly. The cross striations were poorly demarcated. The longitudinal markings stood out somewhat more prominently than the cross striations. Among these fibers were groups of much smaller fibers of from one-third to one-fifth the diameter of the large fibers. The smaller fibers presented numerous sarcolemmal nuclei, which were close together. The general staining reaction of these fibers was somewhat deeper than usual, and much deeper than that of the larger fibers. The cross striations in the smaller fibers also stood out clearly. Occasional groups of muscle cells were of normal appearance. The connective tissue was not increased. In many places there were large fat cells between adjacent bundles of muscle cells, at times extending among the individual muscle fibers and separating small groups from the rest of the fibers. Several sections were entirely free from replacement with fat. No infiltration with lymphocytes or polymorphonuclear leukocytes was seen. There were several small nerves in the sections. These presented no changes demonstrable with hematoxylin and eosin."

COMMENT

Neurons affected by amyotonia congenita present a characteristic appearance, which is easily recognizable. Careful search through sections from various parts of the brain, spinal cord and sympathetic trunk revealed affected neurons in the following locations only: the ventral anterior column of the gray matter (somatic efferent cells); the nucleus of the hypoglossal nerve (somatic efferent cells); the nucleus ambiguus (branchial efferent cells of the vagus and glossopharyngeal nerves); the motor nucleus of the facial nerve (branchial efferent cells); the nucleus of the oculomotor nerve (somatic efferent cells); the globus pallidus (efferent intercalated cells), and the gyrus centralis anterior (giant pyramidal cells of Betz).

The cells in these nuclei resemble one another in the following respects: They are large, multipolar and efferent and have coarse Nissl bodies; the axons of all but the Betz cells and the cells of the globus pallidus end on striated muscle. The axons of the Betz cells end in synapse (directly or through intercalated cells) with the somatic and branchial efferent cells of the cranial and spinal nerves; no tract is known connecting directly the cells of the globus pallidus with the somatic and branchial efferent cells, but the results of this study suggest the possibility of such a connection.

I completed the microscopic study of the nervous system without knowledge of the results of the clinical examinations or the tests for muscle efficiency. When the results of the three methods of investigation are compared a striking parallelism is revealed. The propor-

tion of atrophied cells and cells in the late stages of involvement to cells in the early and intermediate stages was greater in the spinal cord than in the brain stem; conversely, the proportionate number of affected cells in the early and intermediate stages increased from below upward; in the nucleus of the oculomotor nerve, the globus pallidus and the anterior central gyrus all the affected cells were in early or intermediate stages. These facts suggest that the disease progresses gradually from below upward. Support for this hypothesis is furnished by the ratio of normal and affected cells. Cells presenting a healthy appearance were present in each of the nuclei named. The proportion of unaffected to affected cells was least in the thoracic region of the spinal cord; the sacrospinalis muscle, the muscles of the abdominal wall and the diaphragmatic and intercostal muscles are supplied by somatic efferent nerve fibers from cells in this region. Furthermore, unaffected cells were least numerous in proportion to affected and atrophied cells in the medial part of the anterior column of the gray matter in the lumbar and cervical enlargements and in the upper cervical region; the sacrospinalis, splenius, semispinalis and longus colli muscles, all of which are trunk muscles, are believed to be supplied by cells in the medial part of the ventral column; comparison with the cords of other children of the same age showed that the number of large normal cells in the cord of this infant was diminished. The tests for muscle efficiency showed that the muscles of the trunk were weaker than any others; the infant could not move the trunk and could not lift the head when lying either in the prone or in the supine position. The mother observed that breathing was not normal, and the clinical examiner expressed the belief that it was entirely abdominal. Autopsy showed that the abdominal muscles appeared somewhat paler than usual.

The proportion of normal to affected and atrophied cells was higher in the lateral part of the ventral column in the lumbar enlargement, and still higher in the corresponding area in the cervical enlargement, than in the medial part, where the cells for muscles of the trunk are located. Tests for muscle efficiency revealed that the muscles of the thigh, leg and foot were better than those of the trunk and the muscles of the upper extremity better than those of the lower extremity; the hip joint was held partially flexed, indicating weak extensor, or antigravity, muscles. Clinical examination showed that the infant scarcely moved his legs. There was movement, however, in the upper extremities; he reached for toys, and tests for muscle efficiency showed that the muscles were in from fair to good condition.

The ratio of the number of normal to that of affected cells was greater in the nucleus of the accessory nerve than in the medial part of the gray matter in the upper cervical region. The infant could turn the head from side to side and could balance the head on the vertebral column, movements involving the use of the trapezius and the sternocleidomastoid muscles, both of which are supplied by the accessory nerve.

A number of affected cells were present in the nucleus of the hypoglossal nerve, but the percentage of unaffected cells was higher than in the cervical enlargement. No exception in ability to move

the tongue was noted in either the clinical examination or the tests for muscle efficiency; the child could eat and cry normally.

The ratio of normal to affected cells in the nucleus ambiguus was also high. No inability to use the laryngeal and pharyngeal muscles, which are also involved in eating and crying, was noted in the clinical examinations or the muscle tests.

Many affected cells were present in the nucleus of the facial nerve, but the proportionate number of unaffected cells was high. Muscle tests and the clinical examination showed no abnormality; on the contrary, the infant was described as bright and happy. Eating and crying involve also the muscles supplied by the facial nerve.

The nuclei of the abducens and trochlear nerves contained no affected cells, and 7 abnormal cells only were present among hundreds of normal cells in the left nucleus of the oculomotor nerve. No abnormality in movements of the eyes was noted in the clinical examinations or the muscle efficiency tests. The infant could follow objects with his eyes and was much interested in what was going on around him.

On the day before his death respirations were rather noisy and breathing was becoming more difficult, but the infant was happy and was still eating well. The next morning he was discovered to be practically moribund; he was cyanotic and had vomited recently. Probably death came when there were no longer enough normal ventral horn cells for movement of the diaphragm and the intercostal and abdominal muscles. It is possible that even at the time the infant was admitted to the hospital breathing was entirely diaphragmatic and that death occurred when the disease, in its progress upward, had affected a sufficient number of cells in the region of the fourth cervical nerve to cause cessation of efferent impulses over the phrenic nerve.

This case is also of interest with respect to muscle tonus. In a review of the seminar on this subject held in Berne, Switzerland, in 1931, Cobb and Wolff [4] defended the thesis that "tonus," "hypotonus," "hypertonus" and "postural," "phasic," "static" and "kinetic" movements differ in quanity, and not in quality, since all are mediated through the efferent nerve cells which send their axons to striated muscle. The present case supports this thesis. In this infant all these phenomena were present in the muscles of the eyes; only 7 of their efferent neurons were affected. Many affected efferent cells were present in the nucleus of the facial nerve, but a sufficient number of unaffected cells remained to produce all the phenomena; the same was true of the nuclei of the glossopharyngeal, vagus, accessory and hypoglossal nerves. Not enough sound cells remained in the cervical region of the cord to produce "tonus" in the muscles of the neck or upper extremity, but "static" and "kinetic" movements (balancing and turning the head and reaching for toys) were present. Both "tonus" and "static" movements may be said to have been absent in the lower extremity, and "kinetic" movements were present to a slight extent only; in correlation with this, the proportion of sound to affected cells was less in the lumbar than in the cervical region of the cord. All

4. Cobb, S., and Wolff, H. G.: Muscle Tonus: A Critical Review Based on Work Presented at the International Neurological Congress, Berne, Switzerland, 1931, Arch. Neurol. & Psychiat. **28**:661 (Sept.) 1932.

phenomena, including "tonus," were absent in the muscles of the trunk, and the proportion of sound to affected cells was least in the thoracic region of the cord and in the medial part of the ventral column in the cervical and lumbar regions.

It is unlikely that "tonus" is influenced by the autonomic nervous system, since no characteristically affected cells were present either in the intermediolateral column of gray matter of the spinal cord or in the sympathetic ganglia; shrunken, darkly stained cells were present in both the intermediolateral column and the sympathetic ganglia in the present case, but such cells were present in these areas in infants who did not have amyotonia congenita.

Another respect in which this case is interesting is the close resemblance in the distribution of the affected cells to that of the virus and affected cells in cases of poliomyelitis. There is this difference, however: In the present case the thoracic region of the cord and the medial region of the anterior column of gray substance in the lumbar enlargement were the sites of earliest and greatest damage, whereas Fairbrother and Hurst [5] and Brodie [6] observed that the lumbar region of the cord was attacked first and most severely in cases of poliomyelitis. The fact that the somatic efferent cells all along the spinal cord and brain stem and in the globus pallidus are in intimate contact with branches of the corticobulbar and corticospinal axons of the Betz cells suggests that these fibers may serve as the route along which a causative agent may travel upward. In refutation of this hypothesis, however, is the fact that the somatic efferent cells are also in synapse with the fibers of the rubrospinal and vestibulospinal tracts; yet no affected neurons have been observed in either the red or the vestibular nucleus in case 1.

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5. Fairbrother, R. W., and Hurst, E. W.: The Pathogenesis of, and Propagation of the Virus in, Experimental Poliomyelitis, J. Path. & Bact. **33**: 17, 1930.

6. Brodie, M., in Poliomyelitis: A Survey Made Possible by a Grant from the International Commission for the Study of Infantile Paralysis, Baltimore, Williams & Wilkins, 1932, p. 289.

THALAMIC DYSFUNCTION

Report of a Case in Which a Thalamic Syndrome Was Treated by Excision of a Porencephalic Cyst

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The occurrence of a thalamic syndrome in a case of an old cerebral injury at birth and its surgical treatment by removal of a porencephalic cyst have not previously been described. Despite the absence of a pathologic study (as the patient is alive and well), the report of a single case seems desirable at this time because of its unique nature and relevance to the subject of thalamic dysfunction in general. In a recent discussion of porencephaly by Patten, Grant and Yaskin [1] there was no mention of thalamic involvement. Although thalamic dysfunction has been studied by various workers, there has been little agreement on the fundamental issues. It is hoped that the present case may help to clarify the situation.

The thalamic syndrome, as described by Head and Holmes,[2] is characterized by the following features, the individual prominence of which may vary in the particular case: 1. Hemiplegia of varying degree, usually slight, often transient and leaving no contractures.

2. Spontaneous pains and other dysesthesias on the hemiplegic side, often occurring in paroxysms, frequently intractable and often prolonged.

3. Abnormalities of sensation on the affected side. The threshold to all types of stimulation is raised, but once sensation is produced it carries an undertone of unpleasantness, at times amounting to intolerable pain. Superficial sensation is diminished or lost; loss of position sense and deep sensibility is often pronounced. Thermal stimuli in particular may produce unusual reactions. Rarely, some types of stimulation which are recognized as pleasant seem to have greatly enhanced pleasantness.

4. Choreoathetoid movements on the affected side.

REPORT OF CASE

History.—G. J. N., a white woman aged 40, single, was admitted to the Boston Psychopathic Hospital on Feb. 25, 1936, with the complaint of paroxysms of spontaneous pain and the hope of finding how much of the patient's pain was real and how much imaginary. She was the second of nonidentical twins, born by transverse presentation and after much manipulation and instrumentation. There were considerable delay and difficulty before breathing was established.

Early in infancy it was noted that the patient did not use the left arm or leg. In 1900, at the age of 5 years, she was seen at the Children's Hospital, in Boston, where a diagnosis of "old cerebral paralysis" was made and it was

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1. Patten, C. A.; Grant, F. C., and Yaskin, J. C.: Porencephaly: Diagnosis and Treatment, Arch. Neurol. & Psychiat. **37**:108 (Jan.) 1937.

2. Head, H., and Holmes, G.: Studies in Neurology, London, Oxford University Press, 1920, vol. 2, pp. 552-553.

noted that the left arm and leg had been paralyzed "since birth." Palliative surgical procedures were begun at that time to relieve the "multiple contractures." From early childhood the patient was conscious of vague, spontaneous, unpleasant experiences on the hemiplegic side. Hypesthesia had always been present on that side. In 1927 she suffered for several months from paroxysms of severe pain, which were migratory and not constantly localized and defied exact description. The condition was diagnosed as "neuritis" and was treated by removal of teeth and tonsils. In 1933 vague, fleeting pains and other dysesthesias reappeared. There were numbness and tingling of the fingers, hands, shoulders and feet. At times there was a sense of burning. Because of the severity of these experiences the patient spent several weeks in bed.

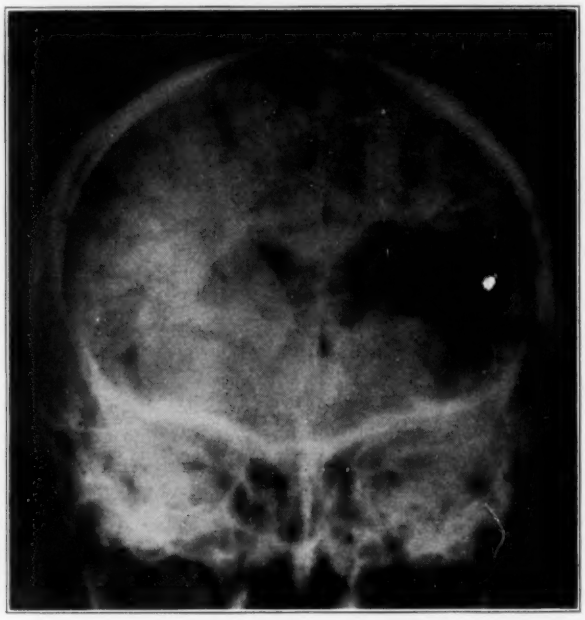
In August 1935 the episode began which resulted directly in the patient's admission to the hospital. The initiating symptoms were confined to the right (nonhemiplegic) side. First, there was a sensation of numbness in the right hand, persisting for several minutes, only to recur later. Then followed pains in the right arm and about the right shoulder. Although the pain was often intolerable, it seemed to be of a strange quality, not describable in terms of the patient's ordinary pain experiences. These acute pains lasted for from minutes to hours, and occasionally all night. Even when the acute pain disappeared, there was always residual steady, dull discomfort. At times the arm felt as though it were going to burst. There were often tingling and numbness of the whole arm. At other times there was a burning sensation in the fingers or in the skin of the forearm or upper portion of the arm. These experiences persisted on the right side until December 1935, when they also appeared on the hemiplegic side. Occasionally the whole left arm "seemed to be on fire." Soon after, pain began to appear in the chest, back and both legs. After particularly severe pains there was a residual burning experience, often lasting for hours. Touching the skin of the left side or motion (active or passive) of the left limb sometimes resulted in similar extreme pain. In emotionally tense situations there was involuntary jerking or twisting of the left arm and leg. When the right arm was used there were associated involuntary jerking motions of the left arm. Since August there had been increasing stiffness of the whole body. In addition, there had been frequent and prolonged spells of coughing associated with spastic sensations in the throat.

Since the age of 7 there had been convulsive seizures, usually nocturnal, characterized by incontinence, clenching of the teeth and left hand and spasms, "mostly in the throat." These occurred from one month to two years apart. In December 1935 a seizure appeared after a free interval of two years.

Despite the patient's physical limitations, she made a fair social adjustment. She completed three years of high school, made friends and in her teens occasionally took care of a neighbor's child for an afternoon. While often cheerful and optimistic, she frequently became depressed, irritable, quarrelsome and unamenable to persuasion. On occasions she manifested considerable emotional instability, flying into severe rages and railing bitterly against her parents. There was probably considerable provocation, but her attitude was nevertheless extreme. Because of her tantrums, irritability and tension, she had spent a period in a sanatorium.

Examination (February 26).—The patient was thin and frail. A large hemangiomatous nevus was present in the left suprascapular region. There was left hemiplegia with shortening of the left arm and leg, both of which showed scars of previous tenotomies for relief from contractures. The right side of the body seemed intact neurologically.

Examination of the cranial nerves showed the following abnormalities: Odors were poorly, and at times not at all, recognized through the left nostril. Vision was poor in the left eye, and the field was generally constricted. The fundi were normal except for a distended vein in the center of the left disk. The left internal rectus muscle was weak, resulting in marked external strabismus. The pupils were normal. The left masseter muscle was weak, and there was hypesthesia of the face, tongue and buccal mucosa on the left side. There were atrophy and paresis of the left side of the face; the forehead was unaffected, however, and there was no ptosis of the left eyelid. Hearing was diminished on the left. Taste was less acute on the left side of the tongue than on the right, and at times was absent. Swallowing and the gag reflex seemed normal. Phonation was unaffected.



Encephalogram showing a porencephalic cyst.

There was weakness of the left sternocleidomastoid and trapezius muscles. The tongue projected in the midline. Speech was not remarkable.

The left arm and leg were shorter than the right and were comparatively atrophic. They were both in a state of considerable contracture, involving especially the hand and foot. They were capable of some voluntary movement but were weak. The gait was uneven, due to spasticity of the left leg and foot, only the toes of which touched the ground in walking.

The tendon reflexes on the left were all hyperactive, except for the ankle jerk, which was limited by the shortened achilles tendon. There was clonus of the ankle, and the foot gave an extensor response to plantar stimulation. The abdominal reflexes were not elicited on this side.

Sensation on the left side was also markedly abnormal. There was severe hypesthesia, but when any sensation was produced it was characterized by an unpleasant, and at times painful, quality. Light touch was not perceived at all.

There was no discrimination between sharp and dull objects. There was no spatial discrimination or appreciation of patterns traced on the skin. Even the anatomic position of the stimulus was not recognized. Deep pressure was perceived only when it was severe enough to produce unpleasantness or pain. Vibration was barely appreciated. Position sense could not be tested because of the contractures. A warm object was not described in thermal terms, but when ice was applied the patient screamed that she was being "burned." When a sharp object was drawn heavily across the midline from either side a markedly disagreeable sensation resembling pain was evoked.

The left limbs could not be tested for coordination because of their partial rigidity and lack of position sense.

Associated involuntary movements of the left arm, in the nature of flexion, abduction and elevation, were elicited by voluntary elevation of the right arm.

During sensory examination of the left side, a jacksonian seizure appeared, lasting about four minutes. First, the fingers of the left hand contracted slowly, after which there was slow flexion at the wrist. The arm then flexed slowly at the elbow and suddenly whipped in front of the body to the right. The head then turned rapidly from side to side and was finally brought forward on the chest. After this the left toes began to twitch; the leg drew up somewhat and became inverted, and there followed a few clonic contractions at the thigh. During this part of the seizure the left arm relaxed and supinated briefly, only to pronate again. The patient was conscious throughout.

A week after encephalographic examination a spontaneous seizure occurred. The patient lost consciousness, became cyanotic and passed into a state of tonic flexion; the head and right eye were turned to the right. There was a Hoffmann sign on the right, but the Babinski sign was not elicited; there was reduplication of the ankle jerks, but no clonus. The pupils did not fail to react. The patient was not incontinent. After the seizure, which lasted for only three minutes, she was confused for about a quarter of an hour.

The mental status was not remarkable. The general behavior of the patient was appropriate in every way. She was friendly, cooperative and sociable and was considered an asset to the ward. The stream of talk was equally normal. She enjoyed conversations and was an interesting raconteur. Her mood was pleasant. In fact, one wondered if her mood was not somewhat elevated—possibly a reaction to being out of her home environment and in new surroundings. There were no distortions of the outside world and no delusions, hallucinations or misinterpretations. The intellectual status seemed intact. She was well oriented, had good memory for remote and recent events, showed good retentive powers and had excellent judgment, facing all the diagnostic and therapeutic features of her case with understanding and equanimity. Insight was equally good. The score in a Stanford test was "inferior intelligence for adults."

Special Procedures.—Laboratory studies of the blood, urine and cerebrospinal fluid gave normal results. Examination of the fluid revealed no cells, a total protein content of 22 mg. per hundred cubic centimeters, no globulin, a sugar content of 67 mg. and a normal colloidal gold curve.

An encephalogram (March 13) disclosed a cyst, the size of a walnut, on the right side, in the region of the island of Reil. It appeared to communicate with the lateral ventricle. The neurosurgical consultant, Dr. Gilbert Horrax, expressed the opinion that it was "almost certainly a porencephalic cyst, due to an injury at birth."

Operation (Drs. Gilbert Horrax and James L. Poppen, at the New England Deaconess Hospital, April 4).—A decision to operate was reached, after much

discussion. No promises were made; the patient readily consented, however, and the operation was undertaken promptly.

A median bone flap was turned down on the right side and the dura reflected upward. "There was immediately apparent on exposure of the cortex a superficial cystic area which, so far as could be told, ran diagonally more or less along the line which ordinarily would be followed by the sylvian fissure, separating the latter. On its surface, it measured from about 0.5 to 1 cm. in width and probably from 4 to 6 cm. in length. It was possible to dissect out the cyst, which had a thick arachnoid wall; as the cortex was brushed away on all sides, it could be seen that the lining extended under the temporal lobe and beneath the cortex on all sides, making a bag-shaped structure, which could gradually be freed from the underlying tissues. By clipping the thick neck of this cyst where it had been freed at the surface, it was finally possible to surround the cyst entirely, not without some difficulty in the anterior and inferior portions of its subcortical area, where there was an interlacing network of arterial and venous radicles, almost like a racemose aneurysm. These, however, could be clipped or coagulated individually and the sac dissected from them.

"It was now seen that the sac communicated anteriorly and posteriorly with the right lateral ventricle by round foramens, which measured approximately 2 by 2 cm. Between these connections with the ventricle there was a wide band of thick scar tissue, which ran from the inferior wall of the ventricle in the region of the optic thalamus to the superior and medial portions of the wall of the cyst and the brain beyond it. This thick band of scar was therefore fairly completely excised; as this was done with the electrosurgical needle, the patient had some twitching of the left side of the body when the excision was being carried out in the region of the floor of the ventricle. Finally, this large piece of scarred subcortical tissue and the whole lining of the cyst were lifted out, leaving a great cavity which was now continuous with the ventricle. The choroid plexus was left undisturbed.

"It is possible from the conditions observed that the band of scar tissue may have exerted some pull on the thalamus of the right side and that this pull may have been transmitted to the left side as well, possibly accounting for the pain."

Postoperative Course and Result.—After a stormy convalescence, the patient was readmitted to the Boston Psychopathic Hospital on May 11, 1936. The most striking feature presented on examination was marked rigidity of the right side, which seemed to be of extrapyramidal type. There was cogwheel resistance on passive manipulation of the arm and leg. The face was masklike, and the muscles were so rigid that the patient was hardly able to open her mouth. There was a variable rhythmic tremor of the right hand and leg. No other impairment of neurologic function on the right side was demonstrated. Possible parkinsonian rigidity on the left side was probably masked by the hemiplegia. There were frequent athetoid movements of the left arm. Occasionally the ocular movements were dissociated. Inconstant nystagmus was noted in the strabismic left eye when it attempted to maintain some degree of fixation to the right. Speech was muttered because of inability to open the mouth adequately. Gait was unsteady because of the bilateral spasticity, pyramidal on one side and extrapyramidal on the other. Neurologic examination otherwise gave essentially the same findings as before the operation. The thalamic type of response to stimuli on the left side persisted, but the paroxysms of spontaneous pain did not appear.

The profound change in the patient's mental state was the other striking feature of the postoperative condition. It was characterized by marked emotional lability and impulsiveness, as well as by considerable motor restlessness. She was

irritable and impatient. She showed no interest in her family or former friends. She seemed depressed and discouraged. Intellectual functions were dull.

She was discharged to return home on May 15. There, the combination of rigidity, explosive emotions and motor restlessness made the nursing problem difficult. Scopolamine hydrobromide, in rather large doses, relieved the rigidity and tremor on the right side fairly rapidly. However, it soon became apparent that the mental status was seriously altered. She would welcome a visitor or relative warmly and a few minutes later order him away, often striking him in the bargain. She could not remain content in one position for any considerable time. She masturbated freely, exposed herself to her father and on one occasion kicked her dog away from his dinner in order to grab it up and eat it herself. She ate all her meals ravenously, stuffing the food into her mouth with both hands. While walking with a nurse she would suddenly fling herself on a neighbor's lawn. She seemed to have lost the power to inhibit, direct or integrate random impulses. While the intellectual status was probably quantitatively reduced in efficiency, it was, nevertheless, relatively well preserved. Memory for both remote and recent events was intact. She was familiar with current events and could perform modest calculations. However, she seemed to have no insight into her changed condition.

By the middle of June 1936, because of her intolerable behavior, it became necessary to place her in a private hospital for mental diseases. The patient continued to receive scopolamine hydrobromide until October 1936. The rigidity on the right side by that time had apparently disappeared, and it did not reappear after withdrawal of the drug. At the time of writing, she has not had any spontaneous pain experiences of the type which led to her first admission to the hospital, and she has not had a single convulsive seizure.

Mentally, the picture has not changed. Intelligence is reported as fair, for at times she plays cards skilfully and otherwise demonstrates her abilities. However, she shows marked loss of self control. Inhibitions seem to have disappeared. There is much motor restlessness. She follows any random impulse. At times she is friendly, and at others, viciously inimical. She is usually babyish in attitude. She is unscrupulous in her methods to gain any immediate end. She lies glibly. At times she is prankish, having on one occasion dumped cold water down another patient's back. She demands and importunes, masturbates openly and eats ravenously. Emotional variability is pronounced. She is sometimes depressed, but at other times hilariously mirthful.

When examined on Jan. 11, 1937, the patient's physical condition, as compared with her previous status, seemed excellent. The mental status was similar to that described in the preceding paragraph. She recognized her former physician and greeted him cordially. She then changed her position in the bed and seemed unconcerned at her complete exposure. Her attitude was babyish and erotic. She insisted that she be taken out at once. She said: "You put me in this place. Take me out now. You're going to take me out now, aren't you? Aren't you?" She was partially uncooperative in a neurologic examination. The stream of talk, while babyish in form, showed no abnormality of content. The answers were concise, precise and relevant. She interjected humorous references. Thus, in regard to her false teeth, she said: "They come out every night, like the stars." Her mood seemed to be elevated and remained so during the examination. She was vivacious and cheerful. There seemed to be no distortion of her relation with her family, the physicians and the nurses. She was correctly oriented. Memory for both remote and recent events seemed intact. However, she showed general slowing of comprehension and retarded grasp of ideas. There

was probably considerable reduction of intelligence, as compared with her preoperative condition, but the variability and general behavior made impossible an exact psychometric study.

Neurologic examination showed that she was entirely free from parkinsonian rigidity on the right side, but that there was persistence of the thalamic type of response to stimuli. Thus, when ice was applied to the left side the sensation was described as "burning" and as "if you put my hand under running hot water." On the right side the ice was recognized as a "cold" object. When a sharp object was drawn across the midline from either side it produced a painful sensation In general, the left side seemed much more hypesthetic than before or immediately after operation.

The patient's condition, then, nine months after operation, can be summarized briefly as follows: She is hemiplegic and hypesthetic and shows persistence of thalamic overresponse and perverted response to appreciated stimuli. The hypesthesia seems to have increased. She is free from parkinsonian rigidity. There has been cessation of the spontaneous paroxysms of pain and the seizures. There has been marked loss of inhibition of impulses and of emotional stability. Intelligence has probably undergone considerable reduction but, as compared with the impulsive and emotional state, is relatively well preserved.

COMMENT

Consideration of some of the questions raised by this case may be of value. The first issue is the theory of thalamic dysfunction. Head and Holmes [3] expressed the opinion that the thalamic syndrome is a release phenomenon. Their view was analogous to that of Hughlings Jackson in regard to motor phenomena resulting from release of control by cortical centers.

> He [Jackson] laid down the law that no destructive lesion can produce a positive effect directly. The activity of the cortex cerebri normally exhibits and controls subcortical motor centers and the destructive lesion sets these centers free to display their powers unchecked. Loss of voluntary power is consequently associated with tonic over-action and an increased reflex discharge in response to afferent impulses.
>
> We [Head and Holmes] believe that an exactly similar condition is revealed on the sensory side of the nervous system by cases of thalamic disease accompanied by an excessive response to peripheral stimuli.

Later, they stated:

> The only function which can be ascribed to these cortico-thalamic paths is that through them the cortex controls, in some way, the activity of the thalamus. If this view is correct, lesions which interrupt these paths, but leave intact the main substance of the thalamus, must lead to a permanent over-activity of functions exercised by that organ. Any afferent impulses, which are capable of exciting this part of the brain, will act on an uncontrolled center and must, consequently, evoke an excessive effect.

Anatomically, it is necessary, according to their view, that all the corticothalamic fibers be cut in order to release the thalamus from control. This is best effected by destruction of the lateral nucleus of

3. Head and Holmes,[2] p. 599.

the thalamus, in which the corticothalamic fibers converge. Cortical lesions would not produce the syndrome because, as fibers run to the thalamus from many points in the cortex, only a relatively small number would be cut off, leaving many still in control.

The authors, however, made a concession.

> It is probable that a subcortical lesion so situated that it destroyed all these paths just before they entered the thalamus might produce the "syndrome thalamique," although the substance of this organ remained intact; but such lesions are rare compared with those which produce this effect by destruction of part of the thalamus itself.

This view of Head and Holmes is open to criticism. Kinnier Wilson [4] has dealt at length with the weaknesses of the theory. It should be noted that most of the discussion by Head and Holmes related to the abnormality of response to peripheral stimulation. Wilson's attack on their theory emphasized particularly the problem of the dysesthesias. It was precisely in regard to this, moreover, that Head and Holmes seemed most unsure of themselves when they wrote: [5]

> The occurrence of spontaneous pains and the painful paræsthesiae of the affected half of the body, so constant a feature of these cases, are due to the uncontrolled activity of this center through which painful stimuli evoke a disagreeable sensation.

This statement requires interpretation. It suggests, on the one hand, that the dysesthesias may be the result of spontaneous "uncontrolled activity" of the thalamus itself and, on the other, that "stimuli" may be responsible. The latter may be a partial anticipation of Wilson's view that the dysesthesias are the result of irritative or destructive influences on the sensory system, either central or peripheral.

In the present case the evidence seems to be against the point of view of Head and Holmes and to favor that of Wilson. As the operation in the present case must have increased any destruction of corticothalamic pathways, it should have resulted, if the theory of Head and Holmes is correct, in aggravation of the syndrome with increase in the dysesthesias rather than in alleviation of the syndrome and disappearance of the dysesthesias.

It is probable that the thalamic syndrome in the present case resulted directly from local mechanical influences exerted by the cyst and the associated bands of scar tissue. This view is supported by the sudden relief produced by the operation.

It should be noted that the operation did not wipe out the entire thalamic syndrome. Only the dysesthesias have disappeared completely. The thalamic mode of response to stimulation persists. This suggests that the dysesthesias were caused by continuously operating influences (pressure of the cyst and traction by the scar tissue) which were terminated by the operation. On the other hand, to explain the persistence of the characteristic thalamic type of response to stimulation we must postulate a stationary anatomic injury to the thalamus.

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4. Wilson, S. A. K.: Modern Problems in Neurology, London, Edward Arnold & Co., 1929, p. 319.

5. Head and Holmes,[2] p. 601.

The bilateral dysesthesias in this case were unusual and require consideration. In harmony with the views already expressed, it seems that the cause was traction exerted from one thalamus to the other. This was the belief expressed by the neurosurgeons. Cutting the scar tissue relieved the traction, and thus the dysesthesias. On the other hand, investigations by Dusser de Barenne [6] suggest an interesting possibility here. By animal experimentation he reached the conclusion that each half of the body surface is sensorially represented in both hemispheres and thalami. Strychninization of one thalamus resulted in bilateral sensory disturbances, both apparently spontaneous and in response to stimulation. He noted, however, that the contralateral side of the body seemed most affected. Whether the present case represents an instance of unithalamic bilateral sensory representation in man is a question. If it does, one would expect to have found on the homolateral side, in addition to the dysesthesias, other evidences of thalamic dysfunction. However, the possibility exists.

The etiology of porencephalic cysts has been discussed by Patten, Grant and Yaskin.[1] They stressed the fact that the cause may vary in different cases. Crothers,[7] Ehrenfest [8] and Ford [9] stressed tentorial tears with hemorrhage from the vein of Galen as a cause both of porencephalic cysts and of hemiplegias at birth. The vein drains the region of the basal ganglia, and injury to it results in venous stasis, anoxemia and ischemic necrosis. The view that cyst formation may follow is supported by a case reported by Beneke and Zausch.[10]

While hemiplegic contractures are unusual in cases of the thalamic syndrome, they obviously represent a quantitative rather than a qualitative feature of involvement of the pyramidal tracts.

The psychiatric aspects of the case are perhaps not unusual. There are numerous reports on the mental status after operations on the brain. Dandy [11] claimed that relatively slight or no involvement of personality resulted from unilateral operations of an extensive nature. Brickner [12] reported on a study of a case in which there was partial bilateral frontal lobectomy. He emphasized that all the changes in the personality and intellect of the patient were fundamentally quantitative rather than

6. Dusser de Barenne, J. G.: Central Levels of Sensory Integration, Arch. Neurol. & Psychiat. **34**:768 (Oct.) 1935.

7. Crothers, B.: Birth Injuries from the Viewpoint of the Neurologist, in Davis, C. H.: Gynecology and Obstetrics, Hagerstown, Md., W. F. Prior Company, Inc., 1934, vol. 2, p. 96.

8. Ehrenfest, H.: Birth Injuries of the Child, New York, D. Appleton and Company, 1922, p. 30.

9. Ford, F. R.: Cerebral Birth Injuries, in Ford, F. R.; Crothers, B., and Putnam, M. C.: Birth Injuries of the Central Nervous System, Baltimore, Williams & Wilkins Company, 1927, pt. 1.

10. Beneke, R., and Zausch, F.: Zwei Fälle von Hirnläsion bei Neugeborenen durch Geburtstrauma, Zentralbl. f. Gynäk. **44**:34, 1920.

11. Dandy, W. B.: Treatment of Ménière's Disease by Section of Only the Vestibular Portion of the Acoustic Nerve, Bull. Johns Hopkins Hosp. **53**:31 (July) 1933.

12. Brickner, R. M.: The Intellectual Functions of the Frontal Lobes, New York, The Macmillan Company, 1936.

qualitative; there was nothing essentially new. He stated that the symptoms were basically intellectual, though sometimes with emotional coloring. In the present case the outstanding change seemed to be at the level of the impulses, and was particularly characterized by apparent loss of inhibition in this respect. There was also unquestionably intellectual impairment, but it was not as striking as the release from inhibition of the patient's underlying personality traits. It is interesting to speculate on the anatomic relations of the brain to the clinical picture in both cases. In Brickner's case, in which there was involvement of the frontal lobes, the resulting clinical picture was primarily intellectual; in the present case, in which there was involvement of the thalamus and the temporal lobe, the resulting clinical picture was primarily one involving the impulses. Here also, the change was one mainly of degree, the patient's family so averring spontaneously.

Consideration of the postoperative changes in personality in the present case strongly supports Cannon's theory of a physiologic antagonism between the "nervous activity of the impulsive thalamic level and that of the conditioning and inhibitory cortical level." [13] Thus, a theory of the corticothalamic control of impulses and emotions seems in harmony with the facts, while one involving sensory experience does not.

Finally, in judging the operative results, one's enthusiasm should be tempered by the consideration that the patient had in the past had rather long remissions from both the seizures and the dysesthesias.

SUMMARY

A case is reported in which a thalamic syndrome appeared late in relation to an old cerebral injury at birth, characterized by the presence of hemiplegia and a porencephalic cyst. Since excision of the cyst and its associated scar tissue (both cortical and subcortical), the patient has become free from dysesthesias and has had no further seizures. Her mental condition has changed profoundly, so that she is lacking in the ability or desire to inhibit random impulses and also shows some intellectual impairment.

Theories of thalamic dysfunction are considered. The facts in this case seem to contradict the views expressed by Head and Holmes and to support a theory of local irritation and destruction. Dusser de Barenne's investigations on animals are considered in the light of the bilateral dysesthesias. The psychiatric features of the case seem to support Cannon's view that the cortex exerts a controlling effect on the functions of the thalamus concerned with emotions and impulses.

NOTE.—Spontaneous reports from the patient and her family over two years after the operation indicate that she has returned to her preoperative level of social adjustment, is as genial and useful a person as she ever was, helps to manage the household and has remained entirely free from dysesthesias and convulsions.

Drs. C. Macfie Campbell, Jackson M. Thomas and William L. Holt gave valuable assistance in the study and preparation of this case.

13. Cannon, W. B.: The Rôle of Emotion in Disease, Ann. Int. Med. **9**: 1453 (May) 1936.

News and Comment

INTERNATIONAL LEAGUE AGAINST EPILEPSY

The annual meeting of the American branch of the International League Against Epilepsy was held in San Francisco on June 7. Officers elected for the coming year were: Dr. Irvine McQuarrie, president; Dr. Edward M. Bridge, first vice president; Dr. Albert W. Pigott, second vice president; Dr. Frederic A. Gibbs, secretary-treasurer, and Dr. Adolf Meyer, vice president for America of the International League Against Epilepsy.

Obituaries

JAMES WRIGHT PUTNAM, M.D.

1860–1938

Dr. James Wright Putnam, emeritus professor of neurology at the University of Buffalo, died at the Buffalo General Hospital on March 23, 1938. He had continued in active practice up to six months prior to his death, but during the last two months was confined to the hospital. Although he realized his condition and was reconciled to his fate, he received his professional friends and colleagues with cheerful greetings and gracious manners that were always his attributes in daily life.

Dr. Putnam was born at Fredonia, N. Y., on June 16, 1860. His father was James Osborne Putnam, the well known chancellor of the University of Buffalo, and his mother was Catherine W. Wright.

After receiving the degree of Doctor of Medicine at the University of Buffalo in 1882, he left shortly to take up postgraduate work in neurology and psychiatry in the clinics of Germany, France and England. Coming under the influence of Charcot, he developed a rare capacity to teach his favorite subject, and on his return to Buffalo was appointed to the chair of nervous diseases at his alma mater. He held this position until 1922, when he became professor emeritus.

Dr. Putnam was a member of the American Neurological Association and was its president in 1903. He was also a member of numerous scientific and medical societies, national and local, and took a keen interest in the programs and discussions. He gave generously of his time to the Buffalo General Hospital, the Buffalo City Hospital and other hospitals where he served on the staff as consulting neurologist. His advice and opinions were eagerly sought on many medicolegal problems, and he served as one of the experts for the state of New York at the trial of Leon Czolgosz, the assassin of President McKinley during the Pan-American Exposition, in 1901.

The medical profession has suffered a distinct loss in the death of Dr. Putnam, whose keen judgment and sound advice made him popular with younger physicians in solving their neurologic problems. He is survived by his wife, Caroline Graves Putnam; three sons, James Osborne, John G. and Roger Wright Putnam, and a sister, Kate E. Putnam.

EDWARD AFFLECK SHARP, M.D.

Abstracts from Current Literature

Physiology and Biochemistry

VESTIBULOCEREBRAL PATHWAYS. J. B. PRICE and E. A. SPIEGEL, Arch. Otolaryng. **26**:658 (Dec.) 1937.

In a previous article Price and Spiegel showed that labyrinthine impulses may reach the cerebral cortex. They now investigate the pathways by which such impulses ascend. Some of these come by way of the cerebellum. The main efferent system of the cerebellum, the brachium conjunctivum, ends partly in the nucleus ruber and partly in the arcuate nucleus of the optic thalamus; thus thalamocortical tracts as well as rubrothalamocortical and rubrocortical tracts provide the final pathway to the cerebral cortex. However, this does not exclude the possibility that other pathways to the cerebral cortex may exist, nor does it prove that synthesis takes place in the cerebellum only.

Price and Spiegel studied the problem by means of the changes in the cortical potentials appearing after stimulation of the labyrinth by rotation after various pathways were eliminated. They first showed that labyrinthine impulses can alter the functional state of the cerebral cortex. They extirpated the cerebellum, except for the flocculi, and found changes in the cerebral cortical potentials similar to those observed in animals with the cerebellum intact. In a previous paper they showed that these changes are prevented by extirpation of the labyrinth. The question then arose as to which extracerebellar pathways conduct the impulses. Magnus and de Kleijn and Rademaker showed that labyrinthine righting reflexes take place after extirpation of the cerebellum and that the center of the labyrinthine righting reflexes is located in the mesencephalon. Their seat is probably not only the nucleus ruber but the reticulate substance in its neighborhood. Experiments of Nishio and Spiegel showed that severance of the posterior longitudinal fasciculus abolishes the labyrinthine righting reflexes. Thus, vestibular impulses may reach the centers for the righting reflexes in the midbrain by way of the posterior longitudinal fasciculus. Therefore the posterior longitudinal fasciculus was severed in addition to extirpation of the cerebellum. After these combined lesions were produced, stimulation of the labyrinth by rotation induced distinct changes in the electrocorticogram. These experiments indicate that the extracerebellar corticopetal conduction of labyrinthine impulses is provided not only by the posterior longitudinal fasciculus but by other systems. Lorente de Nó and Spiegel showed that the posterior longitudinal fasciculus does not represent the only extracerebellar system governing vestibular impulses in a cranial direction. Other tracts outside the cerebellum and the posterior longitudinal fasciculus must exist, carrying labyrinthine impulses to the ocular muscles and to higher cerebral centers.

The experiments indicate that stimulation of the labyrinth by rotation induces a functional change in the cerebellar cortex, as it does in the cerebral cortex after the cerebellum and the posterior longitudinal fasciculus in the anterior third of the pons are destroyed. It is inferred that the labyrinthine impulses may reach the cerebral cortex not only by way of the cerebellum-nucleus ruber system and by connections of the posterior longitudinal fasciculus with the nucleus ruber but also by pathways outside these systems. Vestibuloreticulothalamic pathways and connections between the vestibular and the cochlear tracts are mentioned as possibilities.

HUNTER, Philadelphia.

THE RELATION OF THE MOTOR AREA OF PRIMATES TO THE HYPOREFLEXIA ("SPINAL SHOCK") OF SPINAL TRANSECTION. J. F. FULTON and G. P. MCCOUCH, J. Nerv. & Ment. Dis. **86**:125 (Aug.) 1937.

The temporary suppression of reflex activity caudad to a lesion transecting the spinal cord is due, according to Sherrington, to isolation of the lower spinal seg-

ments from descending pathways. Fulton and McCouch report on the role played in such "spinal shock" by the pyramidal pathways. They used 2 chimpanzees, 4 baboons and 3 macaque, 2 green and 2 red monkeys in their investigation. The motor areas were identified by monopolar stimulation, and various amounts removed with the electrosurgical knife. Transection of the cord was then performed after intervals varying from eight to one hundred and seventeen days. The reflex changes following these procedures were studied carefully, and observations were made on the intervals (1) from the first unilateral ablation to the appearance of reflex activity, (2) from complete transection of the cord to the reappearance of reflexes and (3) from transection to the appearance of equality of reflexes on the two sides.

After the preliminary ablation of the motor cortex, reflexes as well as volitional activity returned earlier in the proximal than in the distal segments of the affected limbs. After spinal transection, on the other hand, the reflexes returned first in the distal segments. All reflexes except the adductor jerk returned after transection of the cord much more quickly in the limbs previously paralyzed by cortical ablation. Primates, with greater cortical development, exhibited greater reflex depression and greater asymmetry. If the interval between the cortical and the spinal operation was long, the asymmetry was slight and more transient. The more complete the cortical removal the longer the reflex asymmetry persisted. In cases in which previous hemidecerebration was done, the asymmetry was much greater than in those in which simple ablation of the cortical motor area was performed. Monopolar faradic stimulation of a pair of posterior roots below the level of an intended transection of the cord gave greater reflex responses from the side previously paralyzed by cortical ablation. Transection had no effect on this asymmetry, though it raised the threshold on both sides progressively to a maximum in about ten minutes after transection. In other words, the "spinal shock" of transection was not immediately evident and required ten minutes for its full development.

Fulton and McCouch emphasize that after a lesion of the motor area the order of reflex recovery is inverse to the extent of previous pyramidal innervation. "The hallux, with its enormous representation in the cortex, is the last member to regain reflex activity." On the other hand, the proximal segments of the limb are last to regain their reflex excitability after spinal transection. The authors believe that this difference is due to the fact that transection of the cord, unlike ablation of the cortical motor area, interrupts "the enormous extra-pyramidal and especially bulbar sources of innervation of the anti-gravity muscles of the proximal segments." They state that "spinal shock" does not appear immediately after transection of the cord possibly because the ether anesthesia removes the suprasegmented centers from activity but leaves the cord free to respond. The progressive development of "spinal shock" for about ten minutes after transection may possibly be attributed to impairment of circulatory function in the cord below the level of transection. The authors emphasize, however, that "there can be no question that the break of neural connections is the major factor in the transient phenomenon of 'spinal shock,'" adding that "a circulatory derangement may be concerned in the permanent isolation dystrophy that so frequently supervenes in primates."

MACKAY, Chicago.

EXPERIMENTAL REFLEX RIGIDITIES. E. G. T. LIDDELL, J. Physiol. **90**:89P (Sept.) 1937.

The rigidity (spasticity) which develops in the limb of a cat after a dorsolateral lesion of the spinal cord is superficially similar to decerebrate rigidity, but is by no means the same, except in the main feature of overactivity in the lower motoneuron arc. The neurologic level whence emanate the differences is above the level of the lower motoneuron. Thus, whereas decerebrate rigidity develops after transection of the midbrain at an intercollicular level, dorsolateral rigidity

is abolished by this transection, but is maintained, or not much impaired, by a suprathalamic decerebration. Moreover, ventrolateral quadrisection of the cord abolishes decerebrate rigidity on that side without impairing dorsolateral rigidity. Decerebrate rigidity, too, is an acute state, while dorsolateral rigidity continues for months, although often masked by voluntary movements. The conclusion is reached, therefore, that connection of the spinal cord with levels higher than the intercollicular level is essential for the maintenance of dorsolateral rigidity. Rigidity of the limbs from cortical lesions is found to be abolished by intercollicular decerebration.

ALPERS, Philadelphia.

THE DISCHARGE OF IMPULSES FROM GANGLION CELLS. J. C. ECCLES, J. Physiol. **91**:1, 1937.

From an analysis of the interval during which an antidromic postganglionic volley can block discharge of the cells of the superior cervical ganglion in response to a preganglionic volley and from the presence of an early break in the curve of facilitation of ganglionic response to two preganglionic volleys, it is argued that synaptic delay is always brief and that discharge is the result of a brief process which spreads decrementally from the region of the *bouton* and usually summates with similar processes spreading from neighboring *boutons* and subsiding before the end of the refractory period. This process is termed the detonator response. The central excitatory state is regarded as a subsequent development serving to lower the threshold of the cell for a considerable interval but not to discharge the cell in the absence of a detonator response. An argument is advanced in favor of the view that the action potential serves as synaptic transmitter of excitation and against the view that acetylcholine plays such a role.

MCCOUCH, Philadelphia.

THE HUMAN ELECTROENCEPHALOGRAM. H. BERGER, Arch. f. Psychiat. **106**:577 (June) 1937.

The present communication brings further proof of Berger's contention that the alpha and beta waves are related to specific layers in the cortex and to specific functions of the brain.

Berger performed a series of experiments with caffeine, sodium salicylate, cocaine, atropine and morphine on subjects in whom these drugs caused cerebral excitation. In all there were a concomitant increase in the beta waves and a decrease in the number and amplitude of the alpha waves. These changes were coincidental with the psychic excitement and increase in the pulse rate.

Berger feels justified, therefore, in restating the point of view expressed in the last communication, which is as follows: Certain beta waves, of which the duration is from 11 to 24 sigmas and the origin in the outer layers of the human cortex, are expressive of psychophysiologic activity in this part of the cortex. They are to be regarded, therefore, as the material concomitants of psychic processes.

W. MALAMUD, Iowa City.

STATIC DISTURBANCES OF POSTURE AND INTERMODAL DISTURBANCES OF PERCEPTION AND THEIR MUTUAL RELATIONSHIP. F. A. QUADFASEL, Monatschr. f. Psychiat. u. Neurol. **96**:326 (Aug.) 1937; **97**:90 (Sept.); 129 (Oct.) 1937.

This article is based on an exhaustive study of 5 patients with symptoms pointing to organic disease of the nervous system of an obscure nature. The patients showed vestibular, cerebellar and migrainous symptoms, which could not be attributed to a single localized lesion. One patient showed evidence of retrobulbar neuritis and involvement of the spinal cord. Attention was focused on a number of striking alterations displayed by all members of the group. These disturbances were summarized as follows: 1. Disturbances in the maintenance of

normal posture. 2. Disturbances of perception consisting of: (*a*) displacement of visual objects from vertical and horizontal planes in a systematic manner; (*b*) distortion of the shape of geometric figures; (*c*) changes in the spatial thresholds for visual and tactile stimuli whereby a number of closely adjacent points recognizable as such by normal persons were perceived as a continuous line, and (*d*) disturbances in the appreciation of brightness in one or both eyes. 3. Attacks in which elementary visual hallucinations, such as dots, moved in a definite direction, with pendulum-like swaying of visual objects occurring in 2 cases. Some of these symptoms have been described previously, and considerable attention has been given to them by von Weizsäcker, Goldstein and Feuchtwanger. The view of von Weizsäcker that they are the expression of a purely functional disturbance is rejected. Quadfasel believes, in agreement with Feuchtwanger, that they are probably based on focal involvement of the brain. This view receives support from observations which indicate that the symptoms under discussion are occasionally unilateral and may occur in patients with frontal and cerebellar lesions.

A mutual relationship between the aforementioned disturbances was demonstrated by Quadfasel. It was shown that postural changes influenced the elementary visual hallucinations and the pendulum-like swaying of objects. For example, changing the position of a limb altered in a regular and predictable way the direction in which the visual hallucinations moved. A similar influence on these movements and on the disturbances of perception was produced by auditory, tactile, visual and olfactory stimuli. Thus, an auditory stimulus might correct or increase the displacement shown by a visual object. Quadfasel records a wealth of carefully made observations along these lines, for details of which the original article must be consulted.

In attempting to understand the phenomena which he described, Quadfasel avoids explanations which go beyond concrete data and seek to connect function and anatomic structure in a confused manner. He refers to similar phenomena noted by other investigators in normal persons under experimental conditions. His observations failed to provide concrete evidence of any general disturbance in the functioning of the brain. The changes involved not every activity of the various sensory systems but only performances which were closely allied to one another. The observations showed that there is a close relationship between the postural disturbances and the alterations of perception. It is suggested that the symptoms may be based on a "tonic" factor in the stimuli. The symptoms occur within a definite, interrelated group of activities from which visual, tactile and "tonic" components can be artificially isolated. Quadfasel agrees with Magnus that orientation of the retina with reference to space perception is conditioned by earlier and simultaneous stimuli which occur in other sensory systems and influence the cerebral cortex. He concludes that perception is not the function of an isolated sense organ nor a diffuse function of the whole brain. The observations demonstrate the complexity of performances which have generally been regarded as elementary phenomena.

ROTHSCHILD, Foxborough, Mass.

SLEEP AND WAKING. L. R. MÜLLER, Psychiat. en neurol. jap. **41**:746 (Sept.) 1937.

Müller states that the presence of catabolic substances, such as hypnotoxins, which act on the cerebrum and produce sleep cannot be substantiated. He has been unable to demonstrate sleep-producing chemical substances. He states that the sleep area demonstrated by von Economo in the transition zone between the diencephalon and the mesencephalon, in the retroinfundibular region, has been confirmed by pathologic and physiologic studies. Müller asserts that the cerebrum is shunted during sleep. He assumes that there must be blocking of stimuli from the surface of the body and the sense organs and interruption of the corticofugal pathways.

ALPERS, Philadelphia.

EVOLUTION OF THE CONCEPTION OF CHRONAXIA: I. NERVOUS SUBORDINATION; II. CHRONAXIA AND CONDITIONED REFLEX. A. CHAUCHARD, Psychiat. en neurol. bl. **41**:321, 1937.

Lapicque showed that the chronaxia of the peripheral nerve in connection with the central nervous system is different from that of the isolated peripheral nerve. He called the first type subordination chronaxia and the second constitutional chronaxia. The higher centers, especially those at the base of the midbrain, influence the chronaxia of peripheral nerves. Subordination chronaxia has no constant values, but varies under the influence of external stimuli (emotions, sensory impulses) and of other nerve centers (hemispheres, cerebellum). Chauchard studied the chronaxia in the crab. The chronaxia of the motor nerve was more than doubled after section of the periesophageal connections. Section between the subesophageal ganglia and the motor nerve produced a second, less marked increase in chronaxia. The experiment demonstrated that the peripheral excitability is subordinated to the action both of the cerebral and of the esophageal ganglia but that the cerebral ganglion is more effective. The next group of experiments was performed with dogs in which the bone over the sigmoid gyrus had been removed in a previous operation. The chronaxia of flexor and extensor muscles of the limb was determined percutaneously. Subsequently, the motor cortex was stimulated percutaneously for from two to three minutes with a current not strong enough to elicit a movement. After such a stimulation the chronaxia was increased in the extensor muscles and decreased in the flexor muscles. The chronaxia returned to normal in fifteen minutes in the extensor muscles and in thirty minutes in the flexor muscles. The last group of experiments was concerned with the influence of the conditioned reflex on the chronaxia. Immediately before and after the conditioned reflex occurred, the chronaxia became considerably increased in the flexor and extensor muscles; during the reflex it was decreased. In the period of inhibition of the conditioned reflex by an interfering stimulus, the chronaxia decreased in the flexor and increased in the extensor muscles. The reaction which was found in the working foot was also present in the opposite limb. The chronaxia of the motor cortex changed simultaneously with that of the muscles of the limb, in exactly the same period and in the same direction. From this experience Chauchard derives the conclusion that the law of isochronism is valid in relation to subordination chronaxia.

LEWY, Philadelphia.

Neuropathology

RESIDUAL LESIONS IN HEALED TUBERCULOUS MENINGITIS. CYRIL B. COURVILLE and HARRISON S. EVANS, Bull. Los Angeles Neurol. Soc. **2**:125 (Sept.) 1937.

Many cases of healed tuberculous meningitis have been reported, especially in the older age periods. In only 2.5 per cent of the cases previously reported, were the patients less than 2½ years of age, while in 30 per cent they were over 20. Courville and Evans report 3 cases in children in which healed tuberculous lesions were demonstrated in the meninges after death. In case 1, that of a Mexican girl aged 7 years, with no history of previous illness, the clinical diagnosis was verified by inoculation of guinea pigs. She died fifteen days after admission to the hospital, and necropsy revealed solitary and conglomerate calcareous tubercles scattered over the dorsolateral surfaces of the cerebral hemispheres. There were also clusters of tubercles in the right lung and adhesions in the right pleural cavity. In case 2 a Mexican boy aged 3 years was found to have tuberculous meningitis and was returned to his home with the prognosis of a probable fatal outcome, although the organism was not discovered in the cerebrospinal fluid. A year later the child had what was thought to be infantile paralysis; later, tuberculous osteomyelitis appeared in both feet and was followed by tuberculosis of the ribs and sacroiliac joints. The boy died of pulmonary tuberculosis, eight years after onset of the illness. Autopsy revealed adhesions about the medulla, with advanced hydrocephalus, but no tubercles in the leptomeninges. A calcified

tuberculoma was observed in the white matter beneath the right cingulate gyrus, and a noncalcified tuberculoma was discovered in the left cerebellar hemisphere. In case 3 a Mexican boy aged 6, with no history of previous illness, presented evidences typical of tuberculous meningitis, a lowered sugar content of the cerebrospinal fluid and increased density of the left hilus in roentgenograms of the chest. Death occurred four weeks after onset of the illness. At autopsy a few miliary nodules were seen in the meninges of the brain, some of which were healed and calcified and contained new-formed bone. A small, noncalcified tuberculoma was present in the genu of the corpus callosum.

Courville and Evans conclude that healing in tuberculous meningitis depends not only on local tissue resistance but on minimal meningeal infection. These cases lend support to the belief that many of the cases in which healing was reported were true instances of tuberculous meningitis, even though the bacillus was not demonstrated during the acute stage.

MACKAY, Chicago.

ROSENTHAL FIBERS IN NON-NEOPLASTIC SYRINGOMYELIA. AMOUR F. LIBER and J. R. LISA, J. Nerv. & Ment. Dis. **86**:549 (Nov.) 1937.

Liber and Lisa report the case of a man aged 38 with syringomyelia, who died of pulmonary, intestinal and peritoneal tuberculosis. The essential neurologic lesions were observed in the spinal cord. At the level of the third cervical segment most of the interior of the cord was represented by a mass of completely amorphous material containing a few erythrocytes, some scattered round cells and macrophages. About this mass "unmistakable" Rosenthal fibers were seen, best demonstrated with the myelin stains. Neighboring blood vessels presented greatly thickened, hyalinized walls which occluded the Virchow-Robin spaces. When these spaces were patent, cellular infiltration surrounded the vessels. Two or three syringomyelic cavities, surrounded by gliosis, extended from the fifth cervical segment to the midthoracic level. The lower thoracic segments of the spinal cord were fairly normal, but in the lumbar region an amorphous mass similar to that present at the third cervical segment was seen. Extensive thickening and fibrosis of all three layers of the spinal meninges served practically to obliterate the subarachnoid space in the cervical and lumbar regions and were present to a lesser degree at the thoracic levels. Fibrotic extensions from the thickened membranes passed into the necrotic areas of the cord above and below the syringomyelic portions.

Liber and Lisa propose the theory that the train of events in this case began with adventitial vascular thickening and blockage of the Virchow-Robin spaces, a process which was assisted by the subarachnoid adhesions. These changes resulted in stasis of the tissue fluids of the cord, destruction of the parenchyma of the spinal cord and glial cicatrization with cavitation. They believe that similar stasis may be induced in some cases by the presence of an intramedullary tumor and that syringomyelia may follow. Developmental anomalies may also play a role.

MACKAY, Chicago.

SOME HISTOLOGICAL CHANGES PRODUCED IN MAMMALIAN BRAIN BY EXPOSURE TO RADIUM. H. A. COLWELL and R. J. GLADSTONE, Brit. J. Radiol. **10**:549 (July) 1937.

The changes in the brain that Colwell and Gladstone observed in their investigation of rat brains after exposure to radium are those of nonsuppurative reactionary inflammation. 1. The immediate effects of irradiation are vascular engorgement and changes in the nerve cells, especially the larger cells of the cortex of the hemispheres and cerebellum, and in the basal ganglia, pons and medulla oblongata. Frequently two adjacent cells of similar type in the same microscopic field exhibit marked contrast in the degree of damage that has been inflicted. 2. With lapse of time no attempt at repair is observed. On the contrary, degenerative changes have taken place in the damaged cells and are progressive. Adjacent cells con-

tinue to show the same contrasts, especially with regard to staining reactions. With the hematoxylin and eosin method the cell body and nucleus of the altered cells stain chiefly deep purple. The stain is diffuse, coloring the broken down granular material of the cell body and chromatin material of the nucleus and the matrix of the cytoplasm and nucleoplasm. 3. The changes are similar to those in areas of hemorrhage or mechanical injury, such as may occur in removal of the brain immediately after death. 4. The vascular dilatation that follows immediately after irradiation is accompanied by escape of red corpuscles. 5. Twenty-four hours after irradiation the initial stages of inflammation of the membranes are accentuated, and there are proliferation of the vascular endothelium and perivascular accumulation of small round cells. There are also signs of localized stases. 6. Evidences of inflammatory reaction, which are seen in the earlier stages, progressively increase with the lapse of time and are attended by disintegration and total destruction of nerve cells and occasional hemorrhages into the nerve tissue and ventricles of the brain; in some situations there are contraction of arterioles, with interference of the vascular supply, and patches of necrosis in the affected areas.

EDITOR'S ABSTRACT.

VASCULAR REACTIONS OF BRAIN IN COURSE OF SOLID AND GASEOUS EMBOLISMS: EXPERIMENTAL STUDY ON CEREBRAL VASCULAR SPASMS. M. VILLARET, R. CACHERA and R. FAUVERT, Presse méd. **45**:1555 (Nov. 6) 1937.

Studies made by Villaret and his associates demonstrate the contrast that exists between intense reactions in the arterioles of the pia mater in cases of solid embolism and the absence of vasomotor response at the time of gaseous embolism in the same vessels. Their experiences with solid cerebral embolism make it possible for them to show in an objective manner a phenomenon the significance of which has often been affirmed and denied in neurologic literature but the existence of which, in the form of spasm of the cerebral arteries, had never been verified. Henceforth, its authenticity cannot be doubted. However, in view of the short duration of the observations and the absence of anatomic controls, the authors regard all physiopathologic deductions on this subject as premature. On the other hand, they stress the importance of their observations to the physiologic problem of cerebral vasomotoricity. They bring proof of the possibility of producing spasms of the cerebral vessels by direct endovascular excitation, just as Riser had emphasized the existence of spasms resulting from exogenic irritation, either mechanical or electrical. Experiments with gaseous embolism of the brain demonstrated, on the other hand, the complete indifference of the arteriolar walls to the embolized air bubbles. The authors were never able to demonstrate cerebral vasoconstriction in this condition. The hypothesis of vascular spasms, often invoked recently to explain the nervous accidents resulting from gaseous embolism, does not seem well founded. The authors further state that they were able to demonstrate in the same animal, first, the complete inertia of an arteriole of the pia mater to gaseous embolism and then the spasmodic reaction of the same vessel to solid cerebral embolism, namely, an injected mass of pulverized pumice. These investigations, nevertheless, make apparent the possibility of an essential phenomenon in the course of gaseous embolism, namely, the circulatory arrest. Provoked by the air, which acts like a tampon and interrupts the circulation of the blood, this arrest elicits temporary ischemia in the arterial region involved, which if prolonged may no doubt cause grave alterations in elements as sensitive as the nerve cells. The authors think that the local mechanism of accidents resulting from gaseous embolism of the brain is cerebral ischemia, which in turn is elicited by gaseous obstruction.

EDITOR'S ABSTRACT.

CASE OF A LESION IN THE RED NUCLEUS. R. STÄHLI, Arch. f. Psychiat. **106**:710 (July) 1937.

Stähli reports the case of a man who was first seen when he was 20 and whose condition was followed for twelve years, when he died after an operation. The

condition started with transitory symptoms of increased intracranial pressure. Gradually, the following symptom complex developed: paralysis of all the extraocular and intraocular muscles, excluding those supplied by the abducens nerve and marked cerebellar ataxia on the right, which was greater in the upper than in the lower extremity with hypotonia of both legs and one arm. Postmortem examination showed gradual occlusion of the aqueduct by what appeared to be a scar-forming process, of unknown nature. The hydrocephalus internus that developed seemed to have been spontaneously relieved by a communication between the dilated aqueduct and the interpeduncular cistern. This process destroyed the left red nucleus and caused degeneration of its oral and caudal communications. Stähli is of the opinion that the hemiataxia on the right side was due to this lesion. The tract of Monakow was destroyed by the process, but in spite of this, there was no increase in tonus; in fact, both lower extremities and the right arm were definitely hypotonic.

MALAMUD, Iowa City.

HISTOPATHOLOGIC NATURE AND PATHOGENESIS OF THE CEREBRAL CHANGES FOLLOWING DELAYED DEATH FROM HANGING. M. FURNKAWA, Psychiat. et neurol. jap. **41**:91 (Nov.) 1937.

Furnkawa reports the changes in the brain of a patient aged 32 who lived seventy hours after hanging and was discovered five minutes after the act was attempted. The brain, studied three hours after death, showed hyperemic pial vessels. There was severe erosion of the cells of the cortex and basal ganglia. This was diffuse in the cortex, but most marked in the third cortical layer. The pallidum was relatively well preserved; most of the striatal cells were gone. The Purkinje cells were degenerated, but the diencephalon, mesencephalon and medulla were well preserved. The ganglion cells showed severe ischemic changes. The vessels were filled with red cells; hyaline thrombi were present in the veins.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

EXOPHTHALMIC GOITER AND PSYCHOSIS. I. BRAM, J. Nerv. & Ment. Dis. **86**:152 (Aug.) 1937.

In 42 of more than 5,000 cases of exophthalmic goiter, Bram obtained a history of psychosis, chiefly of the manic-depressive type. In 12 of the total number, the psychosis occurred in surgically untreated patients, and in the rest, in patients thyroidectomized months or years before. In 10 of the 30 cases of postoperative psychosis, the history pointed to the existence of the psychosis before operation, while in the remaining 20 cases the psychosis appeared for the first time after discharge from the hospital. In all the cases of postoperative onset, despite such residuums of exophthalmic goiter as moderate exophthalmos, tremor, moderate tachycardia with irritable heart, insomnia and fatigability, the basal metabolism rate was not excessive, varying from plus 20 to minus 8 per cent. In not a single instance could the presence of a significant family history of psychosis be determined. Despite the coexistence of the two diseases, no definite causal relationship has been established. A psychosis may be superimposed on preexistent exophthalmic disease, or exophthalmic disease, on a preexistent psychosis. In either event, the complication aggravates the preexisting malady and renders the clinical picture and the prognosis graver. In the event of a psychosis complicating exophthalmic disease, the psychosis becomes the major therapeutic problem; treatment of exophthalmic goiter alone is usually futile.

EDITOR'S ABSTRACT.

PSYCHOLOGICAL FACTORS IN ALCOHOLISM. WALTER R. MILES, Ment. Hyg. **21**:529 (Oct.) 1937.

Alcoholism is one of a series of disorders, of which morphinism is a more, and caffeinism a less, serious condition. Addiction to alcohol ranks with syphilis in

the frequency of its occurrence and in its damage to the human family. Alcoholism is chiefly a mental disturbance. It is predominantly an urban disease in men. Alcoholic psychoses are found primarily in middle life. A study based on first admissions to hospitals for mental disease reveals that alcoholism occurs in 14.4 of 100,000 adults. Wall found evidence of abnormal social and psychologic backgrounds in his group of alcoholic patients. Alcoholic excess appeared in the family history in a high percentage of his patients, and exaggerated emotionality, in one third of the mothers.

In the present group of patients, Miles finds that the men, while fairly capable as shown by their performance with short, easy tasks, lack persistence in motivation and ambition for accomplishment requiring effort. They admit to fewer neurotic tendencies than do average men of their age and social status; they tend to emphasize extrovertive behavior patterns and are inclined to react more to social pressure than to well defined and adequate personal goals. They express more self consciousness than the average person and are deficient in independence. They like to do work in which the objectives are clearly defined and in which they feel certain of successful accomplishment. They avoid work involving difficult and complex problems of judgment and tend to be easily satisfied with their rationalizations regarding these evasions and other escapes. Alcoholism does not appear to be directly inherited, except that it may have its basis in a predisposing sensitive or psychopathic constitution.

Therapy in alcoholism has the same discouraging aspects and presents the same challenging opportunities as therapy in mental disorders in general, although in a somewhat different manner. The discouraging aspects of alcoholism are the frequent recurrence of the condition, the persistence of the personality traits that predispose to it and the general habit formations rooted in the personality and contributed to it by the passive avoidance of realistic effort and active adjustment, which is the very essence of the alcoholic experience. Many forms of therapy have been successful and have their advocates. Psychiatric treatment has as a basic routine a full program of active physical exercise, constructive occupational work and agreeable social relaxation. At the same time, the physical systems are scrutinized, and corrective physiologic and medical measures are instituted as needed. The mental life and experience of the patient are reviewed, and his problems of personality adjustment are attacked in terms of his interest and ability, under guidance, to face them.

CORSON, Stockbridge, Mass.

MENTAL DISTURBANCES DUE TO BROMIDE INTOXICATION. T. H. CHEAVENS, C. F. CARTER and J. S. BAGWELL JR., Texas State J. Med. **33**:375 (Sept.) 1937.

Since November 1933 Cheavens and his colleagues have made a study of all patients admitted to the hospital showing evidence of toxemia. The history of previous administration of bromide, as well as the presence of stupor, confusion, hallucinations and disorientation, has been considered an indication for the laboratory determination of the bromide content of the blood. The authors found significant amounts of bromide in the blood of 23 of 555 patients admitted consecutively. It appears that in the more severe forms of bromide intoxication the symptoms and signs of toxic delirium predominate to a sufficient extent to permit clinical recognition in a considerable number of patients. This is not true in the milder forms of bromide intoxication. Hallucinations were present in 16 of the 17 patients whose blood contained more than 150 mg. of bromide per hundred cubic centimeters; confusion and disorientation occurred in 15. Six of these patients were in some degree of stupor. In the group with less than 150 mg. only 1 patient was found with hallucinations. The others presented essentially the symptomatology of the underlying illness for which the bromide was administered. As the patient with severe bromide intoxication recovers the symptomatology tends to change, with evidence of the underlying illness again coming into prominence. This is particularly true when the underlying illness is a protracted

or severe mental disturbance. When the factor of the underlying illness is excluded, the symptoms are sufficiently uniform to suggest the possibility of bromide intoxication; with the laboratory determination of bromide in the blood there should be little trouble in selecting patients with bromide intoxication in any group with mental disturbances. The neurologic signs did not show the same degree of uniformity and offered little help in making the diagnosis. Defects of speech, disturbances of gait and occasional pupillary disturbances were the most prominent conditions, and were found in only a few patients. One of the most serious objections to continued administration of bromides is that, once toxemia is established, there is great likelihood of a prolonged illness in a hospital for mental disease. There is little doubt that bromidism will cause a much longer illness than intoxications in the other drugs. The most frequent source of bromides in the series is, as usual, the physician's prescription. Since the accumulation of bromide in the body occurs at the expense of the chlorides, the treatment is logically based on the administration of chloride. In addition, the administration of large amounts of water assists in the excretion of bromides and tends to remedy the serious state of dehydration which many patients present. Withdrawal of all sedatives seems to be the best procedure. For the determination of bromide concentration, about 15 cc. of blood is collected by venipuncture, allowed to clot and centrifugated. Five cubic centimeters of the clear serum is removed and added to 10 cc. of water in a small flask; then 3 cc. of a 20 per cent solution of trichloracetic acid is added, shaken and allowed to stand for thirty minutes. This is filtered clear. Standards are prepared by adding 5 cc. each of standards I and II (standard I contains 100 mg. of sodium bromide per 100 cc. of water, and standard II, 200 mg.) to 10 cc. of water. To each standard 3.6 cc. of a 0.5 per cent solution of gold chloride is added, and to each cubic centimeter of the filtrate 0.2 cc. is added. The standard is set at 20 and compared; 100 (or 200, if standard II is used) multiplied by the reading of the standard and divided by the reading of the unknown gives the amount of bromide, expressed as the quantity of sodium bromide in 100 cc. of serum.

EDITOR'S ABSTRACT.

CLINICAL OBSERVATIONS ON SCHIZOPHRENIC DRAWINGS. E. GUTTMAN and W. S. MACLAY, Brit. J. M. Psychol. **16**:184, 1937.

Guttman and Maclay regard schizophrenic art as a "special aspect of the problem of how schizophrenics perceive and express the change in their personality." Illustrations permit some schizophrenic persons to express this change more fully than is possible by movements, writing or speech. Since schizophrenic experiences are complex and "not limited to anomalies in the individual senses," the patient who is driven to tell of his inner change resorts to all the means of expression at his disposal. The relation of the drawings to the content of the psychosis is recorded in 5 cases. Case 1 illustrates the relation between drawings and neologisms. In case 2 the patient used drawing to help herself as well as the physician to understand her distorted visions. The patient in case 3 made no record of her hallucinations at the time of their first appearance; months later, however, when painting was suggested to her, her first desire was to illustrate these original experiences in great detail. Cases 4 and 5 illustrate the development of some characteristic features of schizophrenic style in persons with artistic training.

ALLEN, Philadelphia.

PSYCHOGENIC FACTOR IN ASTHMA. E. B. STRAUSS, Guy's Hosp. Rep. **87**:273 (July) 1937.

Strauss examined 30 unselected patients with asthma with a view to determining the absence or presence of "nervous," psychic or emotional factors in the asthmatic syndrome. Of the 30 patients, the "nervous" element was found to be strongly present in 16, well represented in 9, feebly but definitely represented in 4 and undetected in only 1. 1. In its psychic aspects, asthma may in certain cases

be complex determined, i. e., included in the group of conversion hysterias. 2. A person with the allergic diathesis, whose temperament deviates from the conventional norm of his immediate social group, is likely to acquire the asthmatic syndrome. 3. An asthmatic subject is liable to make the asthma the center of his life, i. e., to acquire and cultivate an "asthmatic" personality. Such a person, by the mechanism of what Kretschmer calls arbitrary reflex reenforcement, can "turn on" his asthma on all occasions, whenever it suits his unconscious or preconscious purposes. 4. Allergic subjects who live under conditions of extreme emotional strain and stress are liable to exhibit the asthmatic syndrome. 5. Asthma in an allergic subject may be part and parcel of a general state of anxiety, the affect, when the tension is high, finding an autonomic reflex outlet. If these conclusions are justifiable, they suggest that psychotherapy, in the widest sense, should reenforce physical methods of treatment, the form of psychotherapy being determined by the history in the case. Analytic psychotherapy appears to be indicated in groups 1 and 5. Patients who fall into group 2 should benefit by a personality analysis, as opposed to an experiential analysis (Kretschmer), and should be taught how to accept and adapt themselves to their own temperamental patterns. In the case of group 4, it will sometimes prove possible, by means of active intervention, to modify the patient's environmental conditions. Patients who fall into group 3 should respond well to suggestive methods, with or without hypnosis.

EDITOR'S ABSTRACT.

RELATIONSHIPS BETWEEN MENTAL DISTURBANCES AND DISTURBANCES IN SPEECH: III. SPEECH DISTURBANCES IN EPILEPTIC PERSONS. ERWIN STENGEL, Jahrb. f. Psychiat. u. Neurol. **54**:177, 1937.

Stengel found that the most common disturbance of speech in postepileptic states was difficulty in finding the correct word or words. There was no difficulty in naming common objects or the parts of the patient's own body, but naming parts of the body of another person could be accomplished only by a process of identification. Occasionally there were observed paraphasias of the type encountered in delirium tremens.

The difficulty in naming objects was manifested by a peculiar and regular electivity, which Stengel believes is based on the state of the ego after the epileptic attack. There was a profound disturbance in the integration of the affect, as well as of the ego and the relation to objects of the outside world. Prolonged sleep following the epileptic attack did not result in complete restitution of integration of the patient's relation to the outside world. The disturbance in this relation is regarded by Stengel as one of the causes of certain characterologic peculiarities of epileptic persons. There was also noted a tendency to extreme politeness, which is regarded as a tendency to overcompensation.

In 2 patients there were definite evidences of depersonalization during the postepileptic state of disturbed consciousness. During the depersonalization there was no doubt that the patient experienced the dissolution of ego integration and the poor object integration as a feeling of strangeness, whereas reintegration of the ego and of his contact with the outside world was experienced as a rebirth and a feeling of entering into a new world. In these cases there was a characteristic association between the reintegration of the ego and of contact with external objects and the patient's capacity to name the objects. Stengel points out that there is a difference between the electivity of the disturbance in naming objects, with preference for the objects belonging to the ego, which is noted in the postepileptic state and the electivity encountered in diseases in which there is a disturbance in the body scheme. In the latter there is a tendency to processes of psychic projection, whereas in postepileptic disturbances of consciousness there is rather a tendency to introversion. This difference seems to indicate that in epileptic patients the more central part of the ego is affected, whereas in patients with a disturbance of the body scheme the more peripheral zones of the ego are involved.

KESCHNER, New York.

Meninges and Blood Vessels

INFECTIONS OF SPINAL EPIDURAL SPACE: AN ASPECT OF VERTEBRAL OSTEOMYELITIS. J. BROWDER and R. MEYERS, Am. J. Surg. **37**:4 (July) 1937.

Browder and Meyers describe seven cases of spinal epidural infection. In five the condition belongs to the group designated as spinal epidural abscess, representing the relatively acute process, and two to the group designated as spinal epidural granuloma, representing the more chronic process. Five patients died, and two are living at present. The clinical picture is fairly constant and, for the more acute forms at least, constitutes a fairly definite syndrome, consisting of a history of a previous infection, boring pain in the spine, radicular pain and, finally, involvement of the spinal cord. In the chronic forms there is less definition of the syndrome, although the features outlined are often represented if an adequate history is obtainable. Consideration of the pathogenesis of the disease reveals two main modes by which the spinal epidural space may be invaded: first, by direct extension from an infection adjacent to the vertebral column and, second, by a hematogenous route from a more remotely situated focus of infection. The authors propose reasons for believing that in cases of this kind there is a zone of metastatic vertebral osteomyelitis, which infection subsequently spreads into the spinal epidural space.

EDITORS' ABSTRACT. [J. A. M. A.]

OTITIC MENINGITIS. DEGRAAF WOODMAN, Arch. Otolaryng. **26**:310 (Sept.) 1937.

Woodman reports a case of streptococcic meningitis which followed mastoiditis complicating scarlet fever in which recovery occurred. The child was given convalescent scarlet fever serum intravenously and intraspinally and sulfanilamide intramuscularly and by mouth, together with repeated blood transfusions. He was admitted to the hospital on the fifth day with the rash and other signs of scarlet fever. The ears showed signs of otitis media. On the sixth day of the illness both ear drums ruptured spontaneously. A simple right mastoidectomy on the sixteenth day revealed free pus and necrosis with erosion of the lateral sinus plate. The left side showed only slight clouding in the region of the antrum. On the fifth day after operation, the temperature rose to 105 F. and culture of the spinal fluid showed Streptococcus haemolyticus. Mastoidectomy done on the left side as a precaution revealed resolving mastoiditis. On the twenty-fourth day of the illness sulfanilamide (15 grains [0.975 Gm.] a day) was started. The temperature fell on the twenty-fifth day, and the meningeal signs began to abate on the thirty-third day. Thirteen blood transfusions (2,040 cc.) were given in eighteen days. Sulfanilamide was found in the urine, but not in the spinal fluid.

HUNTER, Philadelphia.

DOES OPERATIVE FUSION OF TUBERCULOUS JOINTS PRODUCE TUBERCULOUS MENINGITIS? F. L. LIEBOLT, Arch. Surg. **35**:1095 (Dec.) 1937.

Liebolt points out that during the twenty-three year period (from 1889 to 1912) before operative fusions came into use, when all tuberculous patients were treated conservatively, 1,398 persons with tuberculosis were admitted to the hospital on whom no operation other than aspiration was performed. However, 149, or 10.6 per cent, of these patients died of tuberculous meningitis, an average of 6.5 deaths a year. During a similar length of time (from 1912 to 1935) during which operative fusion was performed, 1,752 patients with tuberculosis were admitted to the hospital, on whom 1,941 operations were performed. Only 23 of these patients, however, died of tuberculous meningitis. This is a percentage of 1.3 of patients admitted and of 1.1 of operations performed, with an average of 1 death a year. In 8 of the 23 cases of death occurring between 1912 and 1935, no operation was performed because of the patient's condition at the time of admission and during the stay in the hospital. If these 8 cases are eliminated, the percentage of deaths for the patients who were operated on drops from 1.1 to

0.77. Postmortem examinations were made on all but 4 of the 15 patients on whom operation was performed. The diagnosis of tuberculous meningitis was confirmed in each case. In only 1 patient was the fusion solid—a patient with tuberculosis of the spine; in 4 the status of the joint was not known, and in 18 fusion was not present. This, therefore, is evidence that lack either of operative or of natural fusion of a tuberculous joint is in many cases a predisposing factor to tuberculous meningitis. Surgical intervention in a case of a tuberculous joint does not produce tuberculous meningitis. EDITOR'S ABSTRACT.

SPONTANEOUS INTRASPINAL SUBARACHNOID HEMORRHAGE. HOWARD B. SLAVIN, J. Nerv. & Ment. Dis. **86**:425 (Oct.) 1937.

Spontaneous hemorrhage into the spinal subarachnoid space is extremely rare, only 2 previous cases having been reported. Slavin records the case of a man aged 45, who felt a sudden, severe pain in the left hip and lateral aspect of the left thigh after arising from a chair and walking across a room. The pain was worse when the patient walked or lay down and was least troublesome when he sat erect with the left hip and knee flexed. There were no other symptoms. Kernig's sign was present, and the left knee jerk was absent; otherwise, neurologic examination revealed nothing abnormal. Complete studies of the blood revealed no abnormalities of the bleeding or clotting time. The spinal fluid, obtained by puncture between the fourth and the fifth lumbar vertebra, was grossly bloody on the third day after the onset. Six days later the fluid was xanthochromic, and a spinal subarachnoid block was discovered. The fluid, as observed at subsequent spinal punctures, returned gradually to a normal state, and the block disappeared. For a time there was transient hypesthesia in the left fourth and fifth lumbar dermatomes. The Wassermann and Kahn reactions of the blood and spinal fluid were negative. The blood pressure was not recorded. Recovery was complete in one month. MACKAY, Chicago.

SPONTANEOUS SUBARACHNOID HEMORRHAGE. ABDULLA KARMALLY, Brit. M. J. **2**:962 (Nov. 12) 1937.

A man aged 30 suffered an attack of headache, giddiness and stupor. On examination, the neck was rigid, and the spinal fluid contained blood. Death occurred suddenly on the third day. At necropsy a ruptured, as well as an unruptured, aneurysm of the anterior communicating artery was seen. Neither was located at the bifurcation of the artery. Karmally states that defects in the tunica media do not form a complete explanation of congenital aneurysms because the internal elastic lamina can maintain the integrity of the cerebral vessels in the presence of such defects. Also, the embryologic explanation (Forbus) of the occurrence of such defects as the result of congenital weakness of the walls of vessels near the origin of branches is not always borne out. As in the case reported, aneurysms may occur at some distance from the site of branching. Karmally concludes that further histologic investigation is required before congenital aneurysms can be accounted for satisfactorily. ECHOLS, New Orleans.

LEPTOMENINGITIS WITH LOW LOCALIZATION; CLINICAL AND THERAPEUTIC STUDIES IN FOURTEEN CASES. DEVIC, RICARD and M. GIRARD, J. de méd. de Lyon **18**:577 (Nov. 5) 1937.

Devic and his associates emphasize the increasing frequency of the leptomeningitides among the syndromes of the cauda equina. They report clinical and therapeutic studies in 14 cases. Anatomically, the adherent process is most often encountered in the cystic type. The etiology of these syndromes is not completely clarified; it has never been possible to isolate precisely and incontrovertibly the local or general causes. From the pathogenic point of view, the authors agree

with Bériel that the physiologic process of sedimentation plays a part in the low localization of the infectious process. It is possible to distinguish a clinical form with scant symptomatology, pain being the only symptom. The authors emphasize the information derived from study of the cerebrospinal fluid: presence of hyperalbuminosis and frequent slight cellular reaction. The progress of iodized oil provides in the majority of cases interesting and exact diagnostic data. The mode of progression of the syndrome determines its individuality. The evolution is slow, but capriciously, there are sudden exacerbations and veritable evolutive thrusts, after which there are gradual diffusion and bilaterality of the signs. Phases of remission of several years' duration have been noted. From the diagnostic point of view, identification of the syndrome of the cauda equina in most cases gives no serious difficulties. The true diagnostic problem is the differentiation of tumors of the cauda equina, the leptomeningitides and diseases of the conus terminalis. To differentiate these conditions it is necessary to pay attention to the distribution of the symptoms, the mode of development of the syndrome and information obtained from lumbar puncture and the progress of iodized oil. The therapeutic problem is solved: It is surgical intervention; a more reserved prognosis is indicated for the leptomeningitides than for tumors of the roots. The surgical results obtained by the authors are encouraging. Although occasionally not enough time had elapsed to judge the late results, they obtained a cure in 5 cases, such considerable amelioration as to be almost a cure in 4 cases, the patient generally being able to take up his work again, and arrest of the process in 2 cases, in 1 of which it was partial. Finally, there were 3 postoperative deaths, but in 1 case diabetes was latent. These results, although not perfect, give ample justification for surgical treatment as the only effective therapeutic measure, internal medication and physical therapy being always ineffective. The authors admit that spinal arachnoiditis is a much discussed problem, but in this report they consider only arachnoiditis of the cauda equina. Low leptomeningitis may be associated with forms that are localized higher up. They had occasion to observe 2 cases in which the two localizations coexisted.

EDITOR'S ABSTRACT.

MENINGITIS WITH FRIEDLÄNDER'S BACILLUS. A. SICARD and R. PLUVINAGE, Presse méd. **45**:1800 (Dec. 15) 1937.

According to Sicard and Pluvinage, meningitis with Friedländer's bacillus is rare. It is encountered only about once in one hundred cases of meningitis. It develops in the course of septicemias with other localizations or complicates an infection of the throat, the nose or the ear. The otitides with pneumobacillus are well known. They are extremely painful and are accompanied by an abundant discharge of grayish, fetid, viscous pus. Their prognosis is always grave, not only because they are tenacious and relapsing but because they are complicated by meningitis in about half the cases. The authors review several cases from the literature in which meningitis developed after otitis with the pneumonia bacillus. They further show that in other cases angina may lead to meningitis and cite a case illustrating this. Comparatively mild angina was followed by septicemia with signs of meningitis. The patient died; the cerebrospinal fluid was purulent and contained encapsulated bacilli. Although meningitis as a complication of sinusitis is rare, the authors report a case in which a fistula remained after the surgical treatment of chronic frontal sinusitis. Meningitis developed, and the patient died. Bacteriologic examination revealed the same bacillus in the pus from the frontal sinus, in the cerebrospinal fluid and in the blood. The organism had the characteristics of Friedländer's bacillus. Sicard and Pluvinage discuss the clinical aspects of pneumobacillary meningitis. They say that in exceptional cases the onset may be sudden, a veritable ictus, but that at times it is slow. The meningeal signs vary greatly in intensity. Cutaneous hyperesthesia and disturbances of sphincter control are comparatively frequent. On the other hand, the ocular,

motor and vasomotor disturbances and the signs of cortical irritation are comparatively inconstant. Hemorrhagic manifestations are exceptional. The fever is often moderate. The blood culture is nearly always positive. The authors regard the prognosis of meningitis with the pneumobacillus as grave. When the meningitis follows an infection in the ear or nose, a fatal outcome is the rule. For the septicemic state, chemical therapeutics in the form of colloidal metals or the acridine salts may be used. The authors resorted to ventriculospinal lavage with lukewarm physiologic solution of sodium chloride, to which several drops of methylthionine chloride in a 1:100 solution had been added. This form of lavage was well tolerated in the case under consideration and effected a slight improvement. However, a second lavage was without therapeutic effect; the patient died.

EDITOR'S ABSTRACT.

CASE OF MENINGEAL CYSTICERCOSIS WITH ANATOMICOCLINICAL ARACHNOIDITIS: OBSERVATIONS. T. ALAJOUANINE, R. THUREL and T. HORNET, Rev. d'oto-neuro-opht. **15**:538 (Oct.) 1937.

The case reported was that of a woman aged 25, whose illness had begun two years previously. The first symptom was headache, occurring in crises and accompanied by vomiting. Papilledema, diminished vision, intracranial hypertension and a mildly positive Wassermann reacton of the cerebrospinal fluid were present. After slight improvement resulting from antisyphilitic treatment, the patient's condition grew rapidly worse. Visual acuity diminished, and emaciation increased. Visual acuity in the right eye was reduced to perception of fingers and in the left to light perception; vision was limited to the nasal side. Neurologic examination revealed static and kinetic disturbances of cerebellar type, predominating on the left side, and great enlargement of the ventricles. Suboccipital exploration revealed a parasitic vesicle in the fourth ventricle and a patent sylvian aqueduct. Death from respiratory difficulty occurred seven days after the operation. Autopsy revealed basilar leptomeningitis, extending from the bulb to the cerebral peduncles. The blood vessels were embedded in the thickened meninges and were narrowed by endarteritis; sleeve of lymphoplasmocytic infiltration surrounded the vessels and vesicles. All the ventricles were distended; in the choroid plexuses of the fourth ventricle the layer of epithelial cells was thickened; the villi were enlarged, and blood vessels were more numerous and were surrounded by lymphocytic infiltration.

In all cases of meningeal cysticercosis there is a syndrome of intracranial hypertension, accompanied at times by crises of generalized epilepsy or by tonic crises. The meningeal lesions have a predilection for the basilar region, and this localization is responsible for the internal hydrocephalus. A positive Wassermann reaction is not exceptional in cases of meningeal cysticercosis. Owing to this occurrence and the macroscopic appearance of the lesions, a mistaken diagnosis of syphilis must be avoided. Although the arachnoid or leptomeningeal lesions may be marked, it is surprising how slight is the effect on the subjacent nerve tissue; this fact casts doubt on the allegation, expressed by many writers, that the rich nerve symptomatology is due to meningeal lesions of the arachnoid. Their best argument is the therapeutic effect of freeing the arachnoid adhesions. However, the operative results are inconstant, and the good results from operation may well be due to direct action on the nerve lesions. Alajouanine, Thurel and Hornet believe that when both the arachnoid and the nerve tissue are involved, the latter is the primary lesion and that both arise from the same cause.

DENNIS, San Diego, Calif.

SEROUS MENINGITIS AND DISEASE OF YOUNG SWINEHERDS. HEDWIG FATZER, Schweiz. med. Wchnschr. **67**:709 (July 31) 1937.

Fatzer says that in recent years reports from many countries have mentioned a serous meningitis of unknown etiology and benign course. The disease occurs

almost exclusively in young persons. After a prodromal stage that is characterized by general indisposition and may last several days, fever and severe headache develop, and meningitic symptoms occur, such as: rigidity of the neck, Kernig's sign, constipation, slight albuminuria, changes in the pupils and hypersensitivity. The cerebrospinal fluid is usually clear; in rare cases it is slightly opalescent. However, the cell count is frequently extremely high. The reactions of Pandy and Nonne-Apelt are usually positive, and the mastic and colloidal gold reactions show a meningitic curve. A similar symptomatology is associated with meningitis or meningismus in various diseases, but these forms differ from the cryptogenic form described in that their etiology is known. In this connection the author mentions meningitis in the course of typhoid, pneumonia and malaria. In analyzing the cases of cryptogenic serous meningitis that occurred at the university clinic in Basel, Switzerland, she gives especial attention to 2, which were of the type designated as *maladie des jeunes porchers* (disease of young swineherds). Knowledge of the symptomatology of this disorder is important in that it may readily be confused with influenza or forms of typhoid. It is assumed that the disease of young swineherds (which develops after contact with diseased pigs) is a systemic disease in which the meningitic symptoms more or less predominate. It is probable that there are also abortive forms. Lumbar puncture is the best therapy, and some French authors recommend venesection. The etiology is still unknown. Bacterial, serologic and animal experiments produced negative results. However, French authors have recently isolated a filtrable virus from the blood of a patient with disease of young swineherds. The mode of transmission is still unknown.

EDITOR'S ABSTRACT.

Diseases of the Spinal Cord

POLIOMYELITIS IN LOS ANGELES IN 1934. MARY F. BIGLER and J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **2**:47 (June) 1937.

The epidemic of anterior poliomyelitis in California in 1934 was characterized by clinical features at such variance with those of other epidemics as to suggest that a new disease had appeared. Bigler and Nielsen report four cases in detail and four others briefly to illustrate the typical features. The most striking characteristic was the tendency to polyneuritic manifestations. The onset was frequently with marked pain and muscular tenderness throughout the body and severe hyperalgesia of the skin, so that even light contact with bedclothes became painful. Localized urticaria, a peculiar firm, nonpitting edema, painful muscle cramps and spasms and loss or perversion of sensibility over wide areas were observed in many cases. Flaccid paralysis, often involving one half of the body, was the rule. In spite of the flaccidity, the deep reflexes were not uncommonly preserved, or even exaggerated, and were accompanied sometimes by a Babinski reaction. The electrical responses were often normal. Cerebral involvement was common and produced such symptoms as irrationality, hallucinations, delusions, visual agnosia, diabetes insipidus, somnolence or insomnia and amnesia. Bulbar forms with paralyses of the cranial muscles were also seen. Meningeal irritation was evidenced by headache, stiffness of the neck and the Kernig sign. The spinal fluid was normal in all respects in the cases which the authors described.

The course of the disease was often greatly protracted, with periods of remission and relapse occurring as late as two years after the onset. Some forms of the disease were gradually progressive, although the "almost universal" recovery from paralysis was striking. Postmortem examination in one case revealed that the brain was normal. There was extensive softening of the gray matter of the spinal cord, especially in the lateral horns. In the lumbar region of the cord the posterior horns were selectively involved, and the cells of Clarke's column were largely destroyed. The anterior horn cells were relatively well preserved. There was little secondary scarring. The peripheral nerves showed degeneration of myelin sheaths.

Bigler and Nielsen state that in this epidemic the unusual features were almost all seen in patients over 20 years of age. They leave open the question as to the ultimate nature of the disease and state that it is not settled whether another disease was present with the poliomyelitis.

MACKAY, Chicago.

HYPERTROPHY OF LIGAMENTA FLAVA AS CAUSE OF LOW BACK PAIN. R. G. SPURLING, F. H. MAYFIELD and J. B. ROGERS, J. A. M. A. **109**:928 (Sept. 18) 1937.

Spurling, Mayfield and Rogers state that the ligamenta flava are composed normally of yellow elastic tissue and connect the laminas of contiguous vertebrae. They blend with the interspinous ligament and enter into the formation of the capsule of the joint between the articular facets, and the lateral edge forms the posterior margin of the intervertebral foramen. At times they may undergo hyperplastic change and become so thickened that they encroach on the spinal canal, thereby compressing the spinal cord. This hyperplasia presumably is possible at any level, but the authors' experience with the lesion is limited to the ligaments connecting the fourth and the fifth lumbar vertebra. Seven cases in which this lesion was the pathologic entity form the material for this report. In 6 of the 7 cases the lamina of the fourth lumbar vertebra was likewise observed to be greatly thickened and appeared to be at least a part of the pathologic structure. The duration of symptoms in these cases varied from three months to two years. In 6 instances there had been one or more recessions of symptoms. There had been complete incapacitation for at least three months prior to operation in each case. Pain low in the back was the predominant complaint. Radiating pain into one or both lower extremities was present in all 7 cases. In 6 cases it was unilateral (left), and in 1, bilateral. The pain usually followed the distribution of the sciatic nerve, except in 2 instances in which it was referred to the hip and testis. Objectively, all patients had some degree of postural deformity. A carefully performed neurologic examination is of primary importance in differentiating the syndrome of "low back pain" of extraspinal origin from that of intraspinal disease. When the neurologic examination is even suggestive of an intraspinal lesion, studies by means of lumbar puncture should be made. Fluoroscopic examination of the spine after injection of 2 cc. of iodized poppy seed oil gave final, conclusive proof of the presence and location of the lesion. Treatment of this lesion resolves itself into removal of the involved lamina and ligament. One fatality occurred in the series. Streptococcic meningitis secondary to infection of the wound was the cause of death. If the possibility of a rare catastrophe such as this is barred the operation should incur little risk, since it is carried out under local anesthesia with the minimal amount of trauma and hemorrhage. In the other 6 cases there was prompt relief from symptoms. Pain, except that in or about the operative wound, disappeared within twenty-four hours. The sensory loss was usually restored before the patient left the hospital. Persons with loss of motor power showed normal muscular tone within a few weeks after operation. The 3 men who had complained of impotence stated voluntarily that they were again potent in from one to five days. One patient, with incontinence of urine and a trophic ulcer on the heel, regained sphincteric control by the twelfth day; the ulcer was rapidly diminishing in size and was healed completely four weeks after operation. The first operation was done eight months before the time of writing, and the last, three months before; so the late results cannot be recorded. The history in most instances pointed to trauma, as did the micropathologic study of the specimen. There were no signs of infection, grossly or microscopically. Certainly, neoplastic disease was excluded. There was no roentgenologic evidence of bony disease about the lumbosacral or sacroiliac regions. Direct trauma to the ligament and lamina, either acute or chronic, appears to the authors to be the most likely cause. This supposition is strengthened by the fact that the lesion always occurred at the lumbar spinal joint of greatest mobility. The clinical history in the cases in this series indicates that the pressure on the cauda equina

developed many weeks or months after the onset of backache. The observation fits well with the micropathologic study of the specimen, for all the ligaments showed replacement of the normal yellow elastic tissue with white fibrous tissue in which there were calcareous deposits. EDITOR'S ABSTRACT.

FOUR CASES OF FRIEDREICH'S ATAXIA WITH MENTAL SYMPTOMS IN MEMBERS OF THE SAME FAMILY. E. DE SMEDT, A. DE WULF, DYCKMANS and L. VAN BOGAERT, J. belge de neurol. et de psychiat. **37**:155 (March) 1937.

Mental impairment in cases of Friedreich's ataxia is not unusual, but most authors believe that psychoses are uncommon. De Smedt and his co-workers report 4 cases of Friedreich's ataxia occurring in two families, in each of which there were cases of dementia praecox. No definite hereditary relationship was found between the two conditions. The mental symptoms usually appeared several years after onset of involvement of the spinal cord and cerebellum.

WAGGONER, Ann Arbor, Mich.

Vegetative and Endocrine Systems

MIGRAINE: A DISORDER OF THE SYMPATHETIC NERVOUS SYSTEM. W. H. RILEY, J. Michigan M. Soc. **36**:831 (Nov.) 1937.

In addition to the fundamental and essential condition of migraine (inherited functional disorder of the sympathetic nervous system), Riley mentions: (1) the relation of age to the attacks; (2) the fact that among the exciting causes may be mentioned depressive emotions, such as those associated with worry, anxiety, fear and anger, fatigue, exhaustion, loss of sleep, eyestrain, errors of refraction, excessive use of the eyes and use of the eyes in a bright light; (3) sensitization to certain foods and toxins; (4) increased alkalinity of the blood and, (5) spasm or contraction of the arteries in the meninges and cortical centers of the large brain. The immediate cause of the pain is the contraction and spasm of the meningeal arteries, which pinch the sensory nerves in the walls of the arteries. The spasm of the arteries supplying blood to the various cortical centers is undoubtedly responsible for many other symptoms associated with the headache, such as temporary blindness, homonymous hemianopia, aphasia, temporary loss of sensation and temporary motor paralysis of certain parts of the body. The attacks of severe vertigo which frequently accompany an attack of headache are undoubtedly due to spasm of the arteries and change in circulation in the labyrinth and vestibular apparatus and the connecting neural pathways of the internal ear.

EDITOR'S ABSTRACT.

LAURENCE-MOON-BIEDL SYNDROME. J. R. MUTCH, Brit. J. Ophth. **21**:225 (May) 1937.

Mutch reports a case of the complete Laurence-Moon-Biedl syndrome: moderate obesity, hypogenitalism and hypospadias, mental retardation, polydactyly, syndactyly, atrophy of the optic nerve, macular degeneration and lordosis of the lumbar vertebrae. The visual symptoms appeared late, being first evident at the age of 12. Remission occurred, and vision was apparently normal from 14 to 30 years of age. Unlike the usual state of affairs in retinitis pigmentosa, the patient sees best in a dull light and has no difficulty in finding his way about in the dark. At the periphery the retina appears to be normal, only the macular area being affected; this is not surprising when it is remembered that the macular area is photoptic in function and has a relatively high light threshold compared with the rest of the retina, which is scotoptic in function; in the eye adapted for darkness the macula is about a thousand times more sensitive to light than the fovea. The patient's health at the age of 35 is generally good, aside from occasional headaches, impaired vision and lowered mentality. EDITOR'S ABSTRACT. [J. A. M. A.]

A New Syndrome Apparently Due to Over-Activity of the Posterior Pituitary. E. Idris Jones, Lancet **1**:11 (Jan. 1) 1938.

Jones reports the case of a man aged 26 with intermittent epistaxis and occasional diffuse headaches, who was found to be suffering with hypertension, hyperchromic anemia, achlorhydria and disturbance in carbohydrate metabolism.

The blood count prior to liver therapy was: 78 per cent hemoglobin; 3,400,000 erythrocytes; 1.26 color index, and 2,800 white cells. Six months later the count had increased to: 100 per cent hemoglobin; 5,030,000 erythrocytes; 1.08 color index, and 6,650 white cells. This was accompanied by a corresponding decrease in arterial tension from 190 mm. systolic and 110 mm. diastolic, on April 8, to 130 mm. systolic and 80 mm. diastolic, on September 23, and improvement in the dextrose tolerance curve. From examination of the urine it was possible to prove that a substance or substances were present which could simulate hyperfunction of the posterior lobe of the pituitary. The urine in this case contained a pressor principle which caused persistent elevation of the blood pressure in a cat, and possessed an antidiuretic action on the rat, which was independent of the pressor activity, and a melanosome-dispersing action, as seen in the frog. Furthermore, the pressor principle in the urine was not affected by boiling. The posterior pituitary-like substance in the urine was lessened when the patient improved. Emphasis is placed on the fact that the patient's illness represented a new clinical syndrome—hyperfunction of the posterior lobe of the pituitary gland.

Krinsky, Boston.

Adiposogenital Syndrome and Pigmentary Retinitis (Syndrome of Bardet-Laurence-Biedl). P. Pesme and G. Hirtz, Rev. d'oto-neuro-opht. **15**:257 (April) 1937.

The case reported is that of a boy aged 8½ years with an adiposogenital syndrome, visual acuity of 1/10 in each eye and pigmentary retinitis. The patient's mother was obese and had signs of insufficiency of the anterior lobe of hypophysis and sympathicotonia. The patient weighed 40 Kg. and was 130 cm. in height. Under treatment with extract of the anterior lobe of the hypophysis and with thyroid, adrenal and whole pituitary, followed by the administration of extract of embryonal tissues, a marked improvement in the condition occurred. There were no signs of malformation of the skeletal system or the sella turcica. The sugar tolerance was normal. There was no polyuria, lymphocytosis or disturbance in thermogenesis or metabolism. Opinions vary as to the relation of the retinitis and the adiposogenital syndrome. Zondek expressed the belief that the retinal changes were the result of dysfunction of the hypophysis, an opinion which Pesme and Hirtz think is substantiated by the following facts: The visual cells and the nervous portion of the hypophysis are derived from the cells lining the medullary groove. There are anatomicophysiologic relations between the retina and the hypophysis by way of the tangential nucleus of the hypothalamic region. Excitation of the retina brings about a specific secretion of the hypophysis which acts on the chromatophores and testes of the duck.

Dennis, Wagon Wheel Gap, Colo.

Treatment, Neurosurgery

The Treatment of Myasthenia Gravis. Melvin W. Thorner and Joseph C. Yaskin, Am. J. M. Sc. **194**:411 (Sept.) 1937.

Six patients with myasthenia gravis were treated by various methods. Aminoacetic acid, in daily doses of 15 Gm. for periods varying from two weeks to three months, produced no symptomatic change. The dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate (prostigmin) was given orally and the amount adjusted in each case so that each dose produced an effect lasting from one to four hours. All patients were strikingly benefited. All arrived finally

at the same dose, namely, from five to nine 15 mg. tablets evenly spaced throughout the day. As the function of the myoneural junction is presumed to be dependent on acetylcholine and potassium chloride stimulates the production of acetylcholine in the structures, potassium chloride was tried, with no improvement. Four of 5 patients showed slight but definite improvement with the daily administration of from two to four capsules of ephedrine sulfate containg ⅜ grain (24 mg.). Benzedrine was found useful as an adjuvant to prostigmin. Roentgen therapy given over the thymus gland to 3 patients resulted in no significant change.

MICHAELS, Boston.

CLINICAL OBSERVATIONS ON THE EFFECTS OF CHOLINE COMPOUNDS IN NEUROLOGIC DISORDERS WITH SPECIAL REFERENCE TO MÉNIÈRES'S SYNDROME. MELBOURNE J. COOPER, Am. J. M. Sc. **195**:83 (Jan.) 1938.

Six patients with Ménière's syndrome classified on the basis of arteriosclerosis or vasospasm were treated orally with ethylbetamethylcholine hydrochloride, with an average of from 0.006 to 0.008 Gm. three times a day. They were observed in a total of fourteen severe and two minor exacerbations. Five obtained satisfactory relief from the vertigo, headache, ataxia and nausea. The continued use of choline during intervals of quiescence usually, but not invariably, appeared to prevent the recurrence of exacerbations. No tolerance developed after prolonged administration of the drug. One patient having major trigeminal neuralgia was relieved by taking the drug orally in doses of 0.0166 Gm. three times a day. Another patient with marked peripheral arteriosclerosis and intermittent claudication obtained relief while taking choline preparations.

MICHAELS, Boston.

THE USE OF ADRENAL CORTEX PREPARATIONS IN THE TREATMENT OF ASTHENIA. EDGAR S. GORDON, ELMER L. SEVRINGHAUS and MARIAN E. STARK, Endocrinology **22**:45 (Jan.) 1938.

Gordon and his co-workers report therapeutic results in cases of asthenia with the use of preparations of adrenal cortex and the administration of extra salt. Fifteen patients with long-standing adrenal insufficiency who presented a classic picture of asthenia with a low value for serum sodium and low blood pressure, were treated with both hypodermic and oral administration of extracts of adrenal cortex. The benefits from therapy were transient and variable. A second group of fifteen patients presenting features of asthenia, but whose syndromes were thought to be due to factors other than hypofunction of the adrenal gland were treated by a similar technic. The results in the second group were generally excellent. Good results were obtained from hypodermic injections of extract of adrenal cortex supplemented by the use of sodium salts and ascorbic acid. Subjective improvement was prompt, and the responses of the blood pressure were satisfactory The output of vitamin C was measured; it was found that there was a faulty storage of vitamin C in adrenal cortical insufficiency.

PALMER, Philadelphia

TREATMENT OF ESSENTIAL HYPERTENSION AND DIABETES MELLITUS BY IRRADIATION OF THE PITUITARY AND ADRENAL REGIONS. W. L. CULPEPPER, E. D. MADDEN, E. C. OLSON and J. H. HUTTON, Endocrinology **22**:236 (Feb.) 1938.

The treatment described by the authors is based on the theory that essential hypertension and diabetes mellitus are due to a functional abnormality of the pituitary or adrenal glands and that irradiation can be used to correct this functional disturbance. Thirty-two patients with hypertension and diabetes were treated by irradiation; 9 of these showed improvement in both conditions; 8, improvement in the hypertension only, and 3, improvement in the diabetes only. Treatment was given to 302 patients who exhibited essential hypertension; 134 showed improvement, and 23 others, improvement with later relapse. The authors cite

the cases of 268 patients treated by other physicians, 210 of whom showed improvement in the hypertension. The benefit was much more striking in patients having both hypertension and diabetes. The authors state that hypertension was satisfactorily reduced in about 70 per cent of cases in which adequate treatment was administered and that in about 20 per cent of these there was later relapse.

PALMER, Philadelphia.

TREATMENT OF GENITAL HYPOPLASIA IN THE MALE. H. S. RUBENSTEIN, Endocrinology **22**:243 (Feb.) 1938.

Rubenstein treated eight male patients with genital hypoplasia between the ages of 14 and 33 with a combination of thyroid extract and intramuscular injections of solution of posterior pituitary and the gonadotropic hormone from the urine of pregnancy. The results in the eight cases were satisfactory. The author stresses the importance of the psychic accompaniment of genital hypoplasia. It is urged that the personality as a whole be considered and that feelings of inferiority, backwardness, shyness, overcompensation and depression be treated by appropriate psychotherapy. Early treatment is advisable to forestall skeletal disproportion and persistent hypoplasia, and to avoid the distressing psychologic maladaptation.

PALMER, Philadelphia.

EXPERIENCES IN INSULIN-HYPOGLYCEMIA TREATMENT OF SCHIZOPHRENIA. D. E. CAMERON and R. G. HOSKINS, J. A. M. A. **109**:1246 (Oct. 16) 1937.

A year's experience leads Cameron and Hoskins, of Worcester, Mass., to the belief that the Sakel method is a promising therapeutic approach to the problem of schizophrenia. The method has not yet yielded the high percentage of recoveries claimed from some European centers, but since experience appears to be a considerable factor, they believe it is wise to suspend judgment as to the final efficacy of the method. In view of the well known tendency of the schizophrenic reaction to show considerable fluctuation both in its form and in its intensity, considerable care must be exercised to distinguish between the results of treatment and the endogenous fluctuations. Apart from the value of insulin treatment in immediate alleviation in early stages, there are many questions, such as the permanence of the recoveries, the question of the most favorable type and the light which this method may throw on etiology, which can be answered only after further investigation. Since experience plays such a large role in determining efficacy and in forestalling danger, the method should not be attempted save in an adequately equipped hospital for mental disease or under the immediate supervision of a well trained psychiatrist, who should also be capable of meeting the emergencies that may arise. Treatment of 17 patients has been completed. These patients were treated from five to six times a week over periods that ranged from two to ten months. Two have apparently recovered, and 5 others have shown themselves capable of being at home for varying periods. Five patients showed no improvement. No ill effects were noted in patients whose treatment had been prolonged. When improvement occurs, the first changes consist in an increased interest in the environment. Later there are changes in the formal behavior. Relapses are frequent. Sometimes it is possible to ascribe the relapse to errors in technic, and sometimes it appears to be due to psychologic factors, such as are involved when some one endeavors to probe into the causes of the patient's earlier breakdown while his recovery is still in its early stages.

EDITOR'S ABSTRACT.

THEELIN THERAPY IN PSYCHOSES: EFFECT IN INVOLUTIONAL MELANCHOLIA AND AS AN ADJUVANT IN OTHER MENTAL DISORDERS. C. C. AULT, E. F. HOCTOR and A. A. WERNER, J. A. M. A. **109**:1786 (Nov. 27) 1937.

For all practical purposes, theelin is specific in the treatment of involutional melancholia, the apparent rate of recovery being 92 per cent in the series treated

by Ault, Hoctor and Werner. Massive doses of from 30,000 to 40,000 international units for the first month of treatment accelerate the rate of recovery, the period of hospitalization being reduced to an average of three months. Theelin is indicated for any woman during the climacteric having disturbing mental aberrations, whether mild or severe. Theelin therapy is efficacious in relieving distressing symptoms of the climacteric in other types of psychoses, many patients being improved to the extent of recovery.

EDITOR'S ABSTRACT.

TRYPARSAMIDE THERAPY OF NEUROSYPHILIS AND ATROPHY OF THE OPTIC NERVE. L. L. MAYER, J. A. M. A. **109**:1793 (Nov. 27) 1937.

Of the entire group of 155 patients, Mayer observed 54 from an ocular point of view for at least five years and a few for as long as ten years. In only two eyes, or 1 per cent, did blindness develop, while four eyes lost visual field to a degree. It is not the author's purpose to argue whether these impairments were due to tryparsamide, to the neurosyphilis or to both. However, it must be admitted that the patients were poor risks for any kind of treatment. In view of the fact that the visual acuity and visual fields were decidedly improved in so many instances, it seems fair to state that treatment with tryparsamide under proper control is less dangerous than was at first considered, even if atrophy of the optic nerve has already become apparent. Moore's statement that "tryparsamide is absolutely contraindicated in the treatment of the syphilitic optic atrophies," Stoke's contention that tryparsamide is contraindicated "when disease of the optic nerve is present (not the vascular mechanism)" and the statement of Bluemel and Greig that tryparsamide is "a form of therapeutic dynamite, notable chiefly for its dangers" do not agree with the author's experience. On the other hand, the results reported by many authors agree with his, indicating that "the percentage of danger from tryparsamide is no greater than that from some other preparations, providing the proper precautions are used" and that "the proved therapeutic value of tryparsamide in a disease which is 'a medical emergency' justifies the slight risk." It is evident that a small number of patients with syphilis of the central nervous system have involvement of the optic tracts which may lead to blindness even without specific treatment and that an even smaller number of such patients when given tryparsamide may have subjective or objective signs and symptoms of injury to the optic tracts. Whether this minimal degree of danger is due to a direct toxic effect of the drug on the retina or optic nerves, to a particular sensitivity of the patient to the drug, to the toxic effects of the disease on the optic nerve, to arterial spasm caused by the drug or the disease or to the noxious influence of the treatment for syphilis during a period of low blood pressure, as hypothesized by Lauber, the low incidence of damage fully justifies the use of tryparsamide with proper observation.

EDITOR'S ABSTRACT.

ORAL ADMINISTRATION OF PROSTIGMIN IN TREATMENT OF MYASTHENIA GRAVIS. H. R. VIETS, R. S. MITCHELL and R. S. SCHWAB, J. A. M. A. **109**:1956 (Dec. 11) 1937.

Viets, Mitchell and Schwab present brief histories of 18 patients who have been taking the dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium methylsulfate (prostigmin) by mouth continuously for from one to fourteen months. Some were known to the authors years ago; others have come to the clinic only recently. The former patients were treated in the past with aminoacetic acid, ephedrine and other drugs, often with considerable effectiveness. Since the advent of the prostigmin test of Viets and Schwab, the number of patients entering the clinic has greatly increased, 15 having been added from June 1936 to July 1937. Prostigmin is supplied in tablets of 15 mg. each for oral administration. The authors have employed doses of from 4 to 12 tablets a day. The initial doses are spaced at intervals of four hours, usually with a total of 4 tablets a day. This dose is often too small to maintain muscular efficiency, and it must be increased

to from 6 to 12 tablets in twenty-four hours. A maintenance dose, established in two or three weeks, will average from 4 to 9 tablets a day. For patients taking prostigmin by mouth, the spacing of the doses has been of considerable aid in maintaining muscular efficiency during the waking hours. With 6 tablets a day, the doses are taken at 6 and 9 a. m., 12 noon and 3, 6 and 9 p. m. The dose may be doubled before meals, making an intake of 9 tablets, or 135 mg. of prostigmin, a day for an adult. This has proved to be the common maintenance dose for a severe form of myasthenia gravis. A few patients require 2 tablets at each of the six periods. Unequal spacing in some cases may give the best results. Thirty milligrams of prostigmin administered orally is, in most instances, equivalent to 0.5 mg. of prostigmin in a 1:2,000 solution given intramuscularly. The effect, however, is not so prompt and is less likely to be complete. The response comes in about one-half hour, reaches a maximum in one or two hours and wears off in three or four hours. During this period the paretic muscles regain their power in part or in whole. The visceral disturbances are variable. When disagreeable symptoms are induced by prostigmin given orally, they may be controlled by tincture of belladonna in doses of from 3 to 15 drops or by atropine sulfate, $\frac{1}{200}$ grain (0.3 mg.), given with the prostigmin. Twelve of the 18 patients took belladonna or atropine, the dose varying in amount with the abdominal discomfort. The visceral symptoms are often absent when only 1 tablet of prostigmin is taken at a time.

EDITOR'S ABSTRACT.

INSULIN THERAPY IN ACUTE ALCOHOLIC PSYCHOSES: STUDY OF NINE SUCCESSIVE CASES OF ALCOHOLIC PSYCHOSES TREATED WITH INSULIN. G. W. ROBINSON JR., J. Kansas M. Soc. **38**:463 (Nov.) 1937.

Shortly after beginning the use of insulin in treatment of the withdrawal symptoms of alcoholism, Robinson encountered a case of acute hallucinosis with insomnia, delusions, hallucinations, complete disorientation and occasional attacks of extreme, serious mania. Seven hours after the patient's admission to the hospital and one and one-half hours after the second dose of 20 units of insulin, these symptoms had cleared completely. After this Robinson treated nine patients with acute alcoholic psychoses. Each patient received insulin. From 40 to 50 units of insulin divided into two doses was effective in cases of uncomplicated psychosis, but the amount of insulin indicated in an individual case was that sufficient to produce the desired results. An uncomplicated psychosis responded to the following technic: Twenty units of insulin is given subcutaneously immediately on admission. During the next three hours the patient is urged to drink all the orange juice that can be forced. The second injection of 20 units is given three hours after the first. The minimal requirement of orange juice to prevent reaction from the second dose is at least 30 ounces (900 cc.). Ordinarily, the first dose will have no effect on the patient other than to produce hunger and, therefore, cooperation in the taking of fluids and nourishment. The mental symptoms usually are not improved until after the second injection of insulin. From a half hour to an hour after the second dose the patient begins to quiet and soon falls asleep. Sleep may be fitful for a few hours, but from three to five hours after the second dose the patient falls into a deep sleep, from which he awakens clear. The psychosis may or may not return after this sleep. A small dose of insulin is given shortly after the patient awakens, and thereafter no more insulin is used unless the psychosis returns or the patient is not completely clear. If further injection of insulin is thus indicated, at least four hours should elapse between the awakening and the resumption of treatment, during which carbohydrates are forced by every possible means, and the routine of administering insulin is repeated at the end of this period. Six of the author's patients responded perfectly to treatment according to the technic described. The other three patients had complications, two an infection of the upper part of the respiratory tract and the other syphilis.

EDITOR'S ABSTRACT.

FEVER TREATMENT OF DEMENTIA PRAECOX WITH SULPHUR-IN-OIL. LOUIS B. SHAPIRO and CHARLES F. READ, J. Nerv. & Ment. Dis. **86**:162 (Aug.) 1937.

Shapiro and Read used intramuscular injections of a 2 per cent suspension of sulfur in olive oil in the treatment of dementia praecox. The injections were made under the fascia lata at intervals of three days, eight injections constituting a series. The first dose was 2 cc. of the suspension, and the second, 4 cc.; each subsequent dose was 6 cc. The body temperature was elevated to from 102 to 104 F. after the injection. According to a previous report, 13 of 176 patients with dementia praecox treated over a period of four years showed remissions, and 55 had amelioration of symptoms. In the present article, Shapiro and Read record the results of this method of treatment in 103 additional patients with dementia praecox. The patients had recent, acute psychoses; some showed perplexity and indecision; others, excitement or stupor, and still others, indifference and apathy. "Remissions" were noted in 11 of the 103 patients; "marked improvement," in 19; "amelioration of symptoms," in 35, and "no change" in 38. The small number of patients showing a favorable change in the earlier group (50 per cent) as compared with that in the new series (60 per cent) is attributed to the presence of a chronic form in the former. The authors conclude that therapy with sulfur in oil is a useful adjunct to the treatment of both recent and chronic forms of dementia praecox and is particularly valuable in the management of acutely excited, perplexed and bewildered patients.

MACKAY, Chicago.

NARCOLEPSY AND ITS TREATMENT WITH BENZEDRINE SULFATE. H. ULRICH, New England J. Med. **217**:696 (Oct. 28) 1937.

Ulrich reexamined his patients with narcolepsy who have been treated with benzedrine sulfate for nearly two years. No permanent deleterious effects were noted, and there was no evidence of habit formation. Some of the patients complained of temporary disturbances, including anorexia, especially if the drug was taken before meals. Slight temporary elevation of the blood pressure and of the basal metabolic rate was produced in a few cases, but no permanent effect of that nature was observed. Although the need for caution in the presence of vascular hypertension is emphasized, a case is reported in order to show that hypertension, arteriosclerosis and senility are not absolute contraindications to the use of benzedrine in suitable cases. Loss of weight resulted from the treatment of several obese patients. This is believed to have been due in part to the lessened appetite that may result from the use of the drug and in part to the change from periodic quiescence to a state of greater mental and physical activity. Harm may come from the careless and uncontrolled use of benzedrine in the treatment of narcolepsy, especially in otherwise healthy young persons. Dibenzylcarbinamine, a related compound, was tried in a few cases. It had no beneficial action on the narcoleptic state, and its deleterious effect on the gastrointestinal tract was greater than that of benzedrine. Oral medication with benzedrine sulfate appears to be the only satisfactory method of treatment.

EDITOR'S ABSTRACT.

ARTIFICIAL FEVER THERAPY OF SYDENHAM'S CHOREA. H. W. KENDALL and W. M. SIMPSON, Ohio State M. J. **33**:1097 (Oct.) 1937.

Kendall and Simpson subjected 5 patients suffering from Sydenham's chorea to artificial fever therapy, using the Kettering hypertherm. All experienced prompt cessation of choreiform movements. None has had recurrence. There were 4 girls and 1 boy. The duration of chorea prior to administration of artificial fever ranged from ten days to three weeks in the 4 patients with severe disease, and 1 child had had repeated attacks for one year before artificial fever therapy was given. These patients were given from one to eleven treatments, the average single fever session being three hours, with temperatures from 104 to 105 F. The period of observation extends from six weeks to four and one-half years. In addition to the choreiform movements, 3 patients showed evidence of carditis,

as demonstrated by mitral murmurs, electrocardiographic changes and tachycardia. The mitral murmurs disappeared in all after treatment. The normal cardiac rate and rhythm were restored. Two patients had polyarticular arthritis, which also responded promptly to artificial fever. No other form of treatment was employed. All the children tolerated the treatments well, and none was injured in any way.

EDITOR'S ABSTRACT.

TREATMENT OF SPASTIC PARALYSIS. F. H. MILLS, Brit. M. J. **2**:414 (Aug. 28) 1937.

Treatment of patients with cerebral diplegia and Little's disease should begin early because the spasticity, contractures and psychologic changes are progressive. Attendance at school is forbidden. Electrical stimulation and massage are harmful because they increase muscular tone. Treatments begin with a bath at 37 C. The affected muscles are then gently manipulated, the proximal ones being treated first. This type of stimulus is a powerful inhibitor of muscular tone. When muscular spasm is entirely inhibited, passive movement of the joints may be started without evoking the stretch reflex. The patient watches every motion, and at the same time the attendant says: "I am abducting the shoulder," etc. Only passive movements are used until sensory education is complete. Mills finds that incontinence of urine and feces often disappears when the muscles of the face have been inhibited sufficiently to prevent drooling. Two hundred patients have been treated at the author's clinic. Of these, 50 per cent were at first thought to be idiots, but after treatment only 4 were found to be mentally deficient.

ECHOLS, New Orleans.

INDUCED EPILEPTIFORM ATTACKS AS A TREATMENT OF SCHIZOPHRENIA. L. A. FINIEFS, Lancet **2**:131 (July 17) 1937.

On the basis of the work of Müller, who in 1930 reported recovery in 2 cases of "catatonic schizophrenia" following epileptiform convulsions, von Meduna in 1934 formulated the treatment by which seizures are induced artificially. In 1929 Nyiro and Jablonsky observed frequent remissions in patients with schizophrenia who had convulsive seizures.

Finiefs describes his results with metrazol. All forms of schizophrenia were reported to be improved, and no fatality or complication was observed. The best results were obtained in conditions of from six to twelve months' duration. Febrile conditions and other metabolic disturbances were considered contraindications to this form of therapy.

The technic described suggests the discontinuance of all previous sedatives for a few days before this method is used. Metrazol is injected intravenously once or twice a week, care being taken to allow two seizure-free days between injections. An enema is given on the preceding evening, and the injection is administered at 8 a. m. If 0.5 Gm. does not produce a convulsive seizure, the dose may be doubled and the subsequent injections increased. The largest dose reported is 1 Gm. The seizure usually occurs in from one-half to one minute after the injection; it may last two minutes and presents the characteristics of a grand mal attack. The customary postepileptic confusion makes its appearance, and restlessness may follow. Often the patient falls asleep, and it is best to keep him in bed for the rest of the day. No food should be given for at least four or five hours after the seizure. The number of seizures necessary during the course of this treatment varies, but the average is about 30. If no mental improvement should be noticed after 20 episodes, the treatment should be terminated.

The author believes that this method is especially beneficial in early forms, particularly the stuporous and catatonic types. Although it is admitted that the "treatment is very active and somewhat rough," no deleterious effects were observed, since the patients were carefully selected and were robust.

KRINSKY, Boston.

CONVULSIVE THERAPY IN SCHIZOPHRENIA. HUNTER GILLIES, Lancet **2**:131 (July 17) 1937.

Gillies reports the case of a patient with schizophrenia treated with hypoglycemic shock and subsequent injections of metrazol. A woman aged 33 with schizophrenia was treated for ten weeks by the hypoglycemic shock method, with no improvement. One month after termination of insulin shock therapy, treatment with metrazol was begun; after the second convulsion she began to improve. Seven epileptiform seizures were induced; although the stream of talk had become normal and she no longer had any morbid ideas, apathy persisted.

Gillies' experience with 60 induced convulsions suggests that ill effects are slight. Transient vomiting, moderate tachycardia and thrombosis of the vein into which injection is made occur infrequently. It is his belief that the induced convulsion is "no more dangerous than the idiopathic epileptic fit."

In 54 of 110 cases von Meduna obtained remissions varying in duration from less than six months to more than five years. The beneficial results are attributed to "nonspecific stimulation of cerebral cells which had become functionally inactive." Von Meduna did not see any serious complications in over 1,000 induced convulsions.

KRINSKY, Boston.

TREATMENT OF MENTAL DISEASES BY INSULIN. G. BYCHOWSKI, M. KACZYNSKI, C. KONOPKA and K. SZCZYTT, Encéphale **1**:233, 1937.

The method employed was essentially that of Sakel. Intramuscular injections were not found to be superior to subcutaneous administration. When injections of dextrose were necessary they were given by a two way syringe. In some patients sensitization to insulin took place, and a smaller dose became sufficient to produce shock. The latent period between the injection and the beginning of shock may diminish progressively. Thus, for one patient, who received sixty-five treatments, the dose required decreased from 90 to 40 units and the interval from three hours to thirty minutes. A dangerous complication occasionally noted was spasm of the larynx. Convulsions, movements simulating automatic purposeful gestures, paraphasia and transient paralyses of the cranial nerve occurred before and after the period of coma. During coma the pulse rate was slow. Its rapid acceleration was a danger signal indicating immediate interruption of coma. Eighteen patients with schizophrenia of different types were treated. The results were: complete cure, in seven cases; social cure, in two; distinct improvement, in three; improvement, in three, and no improvement, in three. The patients have been observed for five months.

LIBER, New York.

INDICATIONS FOR INSULIN TREATMENT OF SCHIZOPHRENIA. R. LEMKE, Arch. f. Psychiat. **107**:223 (Nov.) 1937.

Forty-six patients with schizophrenia were treated with insulin. Of these, 25 had an acute disease process (of less than six months' duration), and 21, a chronic. There were 23 men and 23 women. Twelve patients showed good remissions; 12, improvement, and 18, no improvement; 4 died. These proportions, according to Lemke, agree with those reported by a number of other workers. The death rate was somewhat high, but the author believes that when the treatment is carried out according to the instructions originally described, risk cannot be avoided. An analysis of the clinical pictures in all cases showed that, except for the duration of the disease, there were no significant correlations between the clinical picture and the outcome.

Encephalographic studies in all cases revealed that there was a definite relationship between the results of treatment and the severity of the encephalographic defects. Lemke believes, therefore, that the treatment should be preceded by an encephalogram and that when pronounced atrophy is observed the treatment is not likely to be successful.

MALAMUD, Iowa City.

POSSIBILITIES OF COMBINED INSULIN-METRAZOL TREATMENT OF SCHIZOPHRENIA. A. ERB, Klin. Wchnschr. **16**:1762 (Dec. 11) 1937.

Erb shows that the suggestion of the combined insulin-metrazol treatment of schizophrenia raises the question whether the negative results following administration of metrazol or insulin alone can be reduced by trying the other substance or by employing the two substances simultaneously. The author reports experiences with insulin and metrazol, on the basis of which he evolved the following procedure for the combined treatment: In cases of schizophrenia in which the psychomotor manifestations predominate (hypokinesis as well as hyperkinesis), he begins with injections of metrazol. After partial or temporary improvement has been obtained, the metrazol treatment is interrupted and the insulin treatment is begun. In cases of hebephrenia, he begins with insulin treatment. He resorts to metrazol only if after six or eight weeks of insulin treatment there is no psychic reaction whatever. After several injections of metrazol, the insulin treatment is resumed. In several cases of catatonic excitation the treatment was similar to that of hebephrenia. For patients in whom 0.7 cc. (in women, 0.6 cc.) of metrazol does not produce a convulsion, insulin treatment is begun. After the spasmophilic tendency has increased in the course of the insulin therapy, treatment is continued as for hebephrenia.

EDITOR'S ABSTRACT.

INSULIN SHOCK TREATMENT OF SCHIZOPHRENIA. F. G. HALPERN, Chinese M. J. **52**:541 (Oct.) 1937.

Of the patients with schizophrenia treated by Halpern by the insulin shock method, only eight have completed the treatment, while others are still under treatment. The patients were unselected and were taken for treatment without regard to the duration and the type of schizophrenia. Although in five of the eight cases the disease was chronic, the results are encouraging. There has been no fatality, although severe collapse and epileptic fits have been encountered, which, fortunately, could be stopped in time. Half of the patients have had complete remission; one, good remission, one, remission with a defect (that is, with social fitness but remaining schizophrenic changes), and two, partial improvement without social fitness. The paranoid form of schizophrenia gave the best response to treatment. Likewise, two patients with acute schizophrenia reacted well. Less favorable than the reactions to treatment of paranoid and acute schizophrenia were those of two patients with catatonia, in one of whom a good remission, and in the other a remission with residual defect, was obtained. Although the duration of the disease was not longer than in the two cases of the paranoid type, the treatment took much longer to effect remission.

EDITOR'S ABSTRACT.

CONVULSION THERAPY IN PSYCHOSES. P. M. VAN WULFFTEN PALTHE, Geneesk. tijdschr. v. Nederl.-Indië **77**:3010 (Nov. 30) 1937.

Van Wulfften Palthe discusses the symptomatology of schizophrenia and the various methods of treatment, particularly the convulsion therapy by means of metrazol, which he himself employed in 17 cases of schizophrenia. In 13 cases the treatment was completed, and in 11 of these a radical change was noticeable. The patients could be discharged without symptoms. In the 2 other cases, in which the schizophrenia had been most severe, the condition was changed but not improved, even after twenty injections. In 4 other cases the treatment is not yet completed; the time of observation is as yet too short to permit an evaluation. The author says that the rapidity with which the symptoms disappear is surprising and that the manner in which the improvement takes place is different from anything that is ordinarily observed in these cases. Nevertheless, the treatment still has unsatisfactory aspects. To be sure, except for luxation of the jaw and fracture of an arm there were no harmful sequels to 124 induced convulsions, but it has not yet been proved that the brain tissue is not impaired by the convulsions. Moreover, the mode of action is still unknown. The author is of the opinion that the convulsion therapy remains a "heroic" measure.

BENZEDRINE SULFATE AS BRAIN STIMULANT. A. M. MEERLOO, Nederl. tijdschr. v. geneesk. **81**:5797 (Dec. 4) 1937.

Meerloo points out that since Prinzmetal and Bloomberg, in 1935, recommended the use of benzedrine sulfate for the treatment of narcolepsy, the substance has been used widely not only in narcolepsy but in asthma, parkinsonism and mental depression. It is Meerloo's object to direct attention to the dangers involved in the use of the substance. He says that benzedrine is widely used among students, and reports the histories of four students who used it while they were preparing for an examination. The first patient complained that he felt as if he was suddenly "going crazy." Although ordinarily rather calm, he became hyperexcitable, threatened his friends and was unable to sleep at night. The author concludes that benzedrine sulfate may be an effective stimulus in some narcoleptic conditions but that the prolonged use can be harmful, in that it involves the risk of secondary toxic effects. Students should be warned against the use of this stimulant.

EDITOR'S ABSTRACT.

Special Senses

CHRONIC PROGRESSIVE DEAFNESS FROM NUTRITIONAL STANDPOINT. G. SELFRIDGE, Ann. Otol., Rhin. & Laryng. **46**:875 (Dec.) 1937.

During the last year Selfridge studied 5 patients with chronic progressive deafness from the standpoint of their dietary histories. A probable relationship between nutritional deficiencies and chronic progressive deafness is pointed out. The dietary histories of the patients were correlated with studies of the chemical constituents of the blood. The patients were given various vitamin concentrates, including the B complex. The studies indicate that more than one factor may be involved in chronic progressive deafness. Vitamin C deficiency may initiate metabolic disturbances in the bone if there is lack of optimal calcium and phosphorus intake. In the early stages, with beginning loss, the use of vitamin B_1 in solution containing 500 international units, correction of the dietary errors and inclusion of a plentiful amount of vitamin B foods are sufficient to restore most of the hearing. In cases in which the loss extends to 1,024 cycles, the entire vitamin B_2 complex should be used. For changes in the nerve observed in cases of chronic progressive deafness in which the loss of hearing is 25 per cent and more, it seems advisable to use a preparation containing only the vitamin B_2 complex. A relationship of the various vitamins, ductless glands and electrolytes is not to be overlooked. If lack of vitamins of the B complex can explain the changes in the nerve and the vasomotor mechanism, it is probable that lack of vitamin C may explain changes in bone metabolism. Such a hypothesis may be incorrect, since considerable information is needed before interrelationships involved in the control of body metabolism by vitamins, ductless glands and electrolytes are thoroughly understood. Nevertheless, it is obvious that dietary disturbances play an important part in otologic problems.

EDITOR'S ABSTRACT.

DEAFNESS ASSOCIATED WITH MENINGOCOCCEMIA. HARRY LEICHENGER and SOL M. ABELSON, Arch. Otolaryng. **26**:306 (Sept.) 1937.

Deafness associated with meningococcic meningitis has been reported frequently. It is usually considered to be due to a lesion of the auditory nerve, the result of purulent invasion of the auditory nerve. Leichenger and Abelson report a case of meningococcemia. The authors believe that the severe bilateral deafness was due to an exotoxin resulting from the meningitis. The spinal fluid was clear, but under pressure. The patient presented signs of meningitis. Cultures of the blood showed growth of a gram-negative, biscuit-shaped diplococcus belonging to the neisserian group. It is possible that the serum which was injected caused the deafness. The authors consider that the deafness in this case is comparable

with that of the inner ear occurring occasionally in cases of mumps, diphtheria, scarlet fever and tetanus. A nonsuppurative process in the ear, possibly caused by the exotoxin of the meningococcus, seems a reasonable explanation of the deafness in this case.

HUNTER, Philadelphia.

BLINDNESS OF HYPOPHYSIAL ORIGIN: FOUR CASES OF THE ADIPOSOGENITAL SYNDROME, WITH RETINAL DEGENERATION AND MENTAL BACKWARDNESS. P. PESME and G. HIRTZ, Gaz. méd. de France **44**:833 (Oct. 15) 1937.

Pesme and Hirtz recently studied 4 cases of a curious hereditary and familial syndrome that is characterized by adiposogenital dystrophy with mental backwardness and retinal degeneration. The authors describe these cases not only because of their rarity but because they show the role of the hypophysis in the development of the syndrome, particularly the ocular lesions. The authors direct attention to the similarity of the disorder to the Laurence-Biedl syndrome. The condition in the cases described differs from that designated as the Laurence-Biedl syndrome in the absence of malformations of the members (syndactylism or polydactylism). Three symptoms characterize the typical as well as the atypical forms: obesity of the hypophysial type, mental backwardness and retinal disorders. The retinal symptoms are especially noteworthy: In all cases there was degeneration of the retina with discoloration and hemeralopia. One of the patients was given extracts of the entire hypophysis for a year, but this form of treatment failed to produce the slightest improvement. After reexamination it was decided to treat the patient with extracts of the anterior lobe of the hypophysis and with several other glandular extracts (thymus, thyroid, adrenals and total hypophysis). Under the influence of this treatment, the patient lost weight and increased in height; moreover, the genitalia developed to normal size; the hands and fingers, which had been extremely short, assumed normal shape, and the nails lost their friability. The mental aspects likewise changed in that the boy became more active and bright. Even more remarkable was the change in the ocular defects. The boy was able to fix his vision without being disturbed by nystagmus, and the photophobia disappeared. Measurement of the visual acuity revealed hardly any increase, but the boy was better able to utilize his visual powers. On the basis of this observation, the authors conclude that the hypophysis influences not only the fat metabolism and the development of the genital organs but also the retina. Such a relationship between the retina and the hypophysis had already been suggested by other investigators, and the authors think that treatment with hypophysial hormones may prove valuable in some congenital retinal defects.

EDITOR'S ABSTRACT.

CONGENITAL NYSTAGMUS AND DISTURBANCES OF NYSTAGMUS PROVOKED EXPERIMENTALLY. JEAN-SÉDAN and G. E. JAYLE, Rev. d'oto-neuro-opht. **15**:529 (Oct.) 1937.

Those who have studied congenital nystagmus are in agreement on only one point: the absence of vestibular disturbance. Jayle and Grisoli (*Rev. d'oto-neuro-opht.* **15**:204 [March] 1937) reported a case of congenital nystagmus in which vestibular examination revealed anomalies. Two additional cases are now reported. The spontaneous nystagmus observed in these cases was characteristic: variability in rhythm, frequency and direction of the movements of the eyes. To these characteristics were added: extreme rapidity of the nystagmus, which became slower when the direction of gaze was changed; variability in the effect of convergence on nystagmus; transformation of the nystagmic movements by optical means, and association of nystagmus with other disturbances of the ocular static, revealed monocular vertical strabismus and associated head movements.

Vestibular disturbances are manifested under two forms: In the first group the provoked nystagmus is modified by the antagonism of the congenital and the provoked nystagmus. This effect varies from one patient to another. In the

second group there appear anomalies in the results of the rotatory and galvanic tests, pointing, perhaps, to a central cause. Horizontal nystagmus is rarely disturbed. Provoked rotatory nystagmus is replaced by horizontal nystagmus; provoked vertical nystagmus is prolonged. These anomalies resemble those found in certain truncal lesions; they may even be traceable to anatomic anomalies of the pathways.

DENNIS, San Diego, Calif.

SYNDROME OF LABYRINTHINE GLAUCOMA. H. TILLÉ, Rev. d'oto-neuro-opht. **15**:577 (Nov.) 1937.

Tillé reports three cases of labyrinthine vertigo in adults, the patients being aged 83, 60 and 45, respectively. The first patient had had chronic glaucoma for twenty years, latterly associated with vertigo, tinnitus and deafness of the senile type. Vertiginous attacks appeared in crises, and vestibular examination suggested dissociation of the caloric and rotatory reactions. The labyrinthine syndrome is probably related to hypertension of the labyrinth, comparable to that found in the eye in glaucoma. The second patient had attacks of vertigo and falling and a lowered upper tone limit. The labyrinths were hyperexcitable. There had been chronic glaucoma for three years in the right eye and for ten years in the left eye. The left eye was completely blind; ocular tension was 60 mm., and the fundus was not visible on account of edema of the lens and media; the right eye had a tension of 35 mm.; the visual field was retracted to the isopter of 15 degrees, and there was a lunated annular scotoma. In the third case the otitic symptoms were evidently caused by syphilis. Diffuse syphilitic cochleovestibular labyrinthitis, deafness for high tones, tonal islands and dissociation of the caloric and rotatory reactions were observed.

Three types of the syndrome are described: (1) senile deafness and visual difficulties resulting from insufficiency of the capillary circulation; (2) syphilitic labyrinthitis in young persons with glaucoma, and (3) labyrinthine glaucoma due to cold edema of the endolabyrinth. In a large number of cases Quincke's edema is associated with glaucoma, but the triad of glaucoma, labyrinthine disturbances and Quincke's edema has not been reported. Until means of measuring the tension of the endolymph and the auditory artery have been devised, it will not be possible satisfactorily to distinguish labyrinthine glaucoma. It is not possible to differentiate glaucoma and stasis in the labyrinth, as may be done in ocular pathologic conditions.

DENNIS, San Diego, Calif.

RECURRING, TRANSITORY HEMIANOPIA FROM CORTICAL AND RETINAL ANGIOSPASM, OCCURRING AT THE MENSTRUAL PERIOD IN A PATIENT WITH SYPHILITIC ARTERITIS AND HYPERTENSION. JEAN SÉDAN, Rev. d'oto-neuro-ophth. **15**:591 (Nov.) 1937.

The case reported was that of a woman aged 41 who at the beginning of three menstrual periods experienced crises of transitory hemianopia. The crises were preceded by erythropia and accompanied by frontoparietal headache and vertigo. They lasted from fifteen minutes to two hours; return of normal vision was preceded by a shower of muscae volitantes and a sensation of euphoria. In two crises there were absolute right hemianopia and relative blindness in the inferior left quadrant. Ophthalmic examination revealed images of both transitory and permanent lesions of the fundi; the former were represented by retinal angiospasm (moniliform arteries), and the latter, by crushing of the veins at the arteriovenous crossings, arteriosclerosis and arteries of whiplash and corkscrew shapes. The retinal angiospasm persisted for some time after the hemianopia disappeared, indicating the greater importance of the angiospasm in the cortex and the posterior ocular pathways in production of the hemianopia. In the last crisis erythropia was experienced in the blind visual sector and persisted after vision returned. The Bordet-Wassermann and Hecht reactions of the blood were positive. Energetic antisyphilitic treatment resulted in cessation of the attacks and marked improve-

ment in the nephritic, cardiac and hypertensive signs. That all the vascular tunics must have been altered by syphilis explains the rare association of retinal and cortical angiospasms.

DENNIS, San Diego, Calif.

ALTERATIONS IN VISUAL FUNCTION IN CASES OF LESION OF THE LEFT OCCIPITAL LOBE. M. BALADO, E. ANDROGUÉ and E. FRANKE, Arch. argent. de neurol. **15**:19 (July) 1936.

The authors report twenty cases of lesions of the left occipital lobe. They conclude that the fibers of the optic radiation may be divided into three parts: The superior part carries fibers corresponding to the superior portion of the retina, the inferior part, fibers corresponding to the inferior portion and the middle part fibers from the macular area. The portions of the optic radiation that are closest to its upper and lower borders terminate in the lips of the most anterior part of the calcarine fissure, while fibers progressively deeper in the radiation terminate more and more posteriorly. When the fibers arrive at the visual area, they pass into this region and terminate in the granular layers lying on either side of it. The authors believe that the part of the granular layer lying over the stria of Gennari corresponds to the homolateral retina and the part lying under the stria, to the contralateral retina, and that the fibers terminate in both in a pattern that is geometrically similar to the pattern of the retina. They think that other fibers from the visual area pass back through the stria of Gennari to reach the visual association areas. They believe that a tract leaves the visual area of one side to pass to the visual area of the opposite side by way of the tapetum, the forceps major and forceps minor and the corpus callosum, where it lies between the commissure of the fimbria and the commissure of the parietal lobe. They report two cases in which there was degeneration of the fibers in the right tapetum following destruction of the bulk of the left occipital lobe.

NORCROSS, Philadelphia.

Experimental Pathology

ABSORPTION OF THE POLIOMYELITIS VIRUS BY CHOLESTEROL. J. A. TOOMEY, Am. J. Dis. Child. **54**:1272 (Dec.) 1937.

Toomey injected a mixture of commercial cholesterol and 1 per cent potent purified poliomyelitis virus of the Flexner M. V. strain intracerebrally into 5 Macacus rhesus monkeys; in 1 animal transient paresis of both legs developed on the eighteenth day, the others being practically unaffected. In all 5 monkeys used as controls, which were given the same amount of the virus without cholesterol, quadriplegia developed. In experiments with single pairs of monkeys, essentially the same results were obtained with the Australian, Trask, Kramer and W. E. strains.

WAGGONER, Ann Arbor, Mich.

THE CALCIUM DEPOSITS IN NERVE CELLS OF WHITE RATS AFTER INJECTIONS OF UREA AND CHOLESTEROL. ROSS C. MACCARDLE, Anat. Rec. **67**:81 (Dec.) 1936.

In rats receiving large daily injections of either cholesterol or urea weakness and paralysis developed. On histologic examination intracellular deposits of calcium were observed in the ganglion cells of the medulla and in the motor cells of the spinal cord.

RIOCH, Boston.

EXPERIMENTAL STUDY OF INVOLUNTARY MOVEMENTS. NATHALIE ZAND, Rev. neurol. **68**:601, 1937.

In a group of eight rabbits a needle was inserted into the dorsal portion of the medulla, and a drop of paraffin was injected. Each rabbit was then killed, and

the medulla was examined microscopically to determine the region damaged. In four rabbits the vestibular nuclei, the posterior longitudinal bundle, the descending tract of Deiters, the substantia reticularis, the predorsal bundle and the root fibers of the sixth and seventh nerves were injured. The result was a variety of tonic and clonic responses, including bilateral hypertonus of the extensor muscles of the neck and body, tremors of the ears, nodding and rotating movements of the head and myoclonus, followed by "pseudovoluntary" movements, such as blinking and vertical position of the ears, as in listening. Only the right Deiters tract was injured. Zand concludes that this tract controls both sides of the body. Twenty-four hours after the operation all the disturbances had disappeared, except slight pleurosthotonos and deviation of gait toward the left. In a second group of rabbits the needle did not reach the medulla, and the paraffin was injected into the meninges. Hemorrhages within the brain stem injured the rubrospinal tract, the ventral and dorsal spinocerebellar tracts and the spinal root of the trigeminal nerve. The involuntary movements consisted of tremor of the tail and the pelvic limb, rhythmic blinking and rhythmic torsion of the ear about its long axis at the rate of 60 per minute, synchronous with the blinking movements. Later there appeared horizontal nystagmus and rolling movements of the body toward the right, about the long axis. When the animal was held by the ears the trunk curved so that the mouth touched the right hip. Hyperextension of the limbs was attributed to a crossed lesion of the rubrospinal tract, releasing the action of the bulbar olive, which Zand believes to be the "tonic center in the hindbrain" hypothesized by Rademaker. Injection of strychnine, or simple puncture of the medulla without injection of foreign substance, gave results similar to those from injection of paraffin. Nodding or "affirmative" movements are thought to be "graticeptive" reflexes and movements of "negation" or lateral rotation of the head to be nociceptive and intended to remove a noxious agent in the mouth or nose. These and other movements noted in the present experiments are believed to have been provoked by section of proprioceptive reflex arcs.

LIBER, New York.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

MEYER SOLOMON, M.D., *President, in the Chair*

Regular Meeting, Jan. 20, 1938

STUTTERING AS A DISORDER OF EMOTIONAL BEHAVIOR AND PERSONALITY. DR. MEYER SOLOMON.

Stuttering is a specifically conditioned disorder of personality, emotive behavior and speech in a struggle for equilibrium during social speaking. Many factors may be responsible for the state of excitement at the first moment of stuttering and for its continuation. In each case careful consideration of all internal and external factors responsible for the onset and continuation of stuttering is essential; they include: the physical condition; the daily program and habits; the makeup and problems of the personality, and the living conditions and personalities in the home, neighborhood, school and workshop. Impartial search must be made for causes of undue pressure during social speaking. Treatment must be that of the total personality, not merely of the speech phenomena; proper management is a combination of physical and mental hygiene and therapy directed toward the physical, mental and environmental problems of the individual patient.

There are many opportunities for research concerning the origin, prevention and treatment of stuttering and its relation to psychologic and psychopathologic problems and the disorders of personality.

DISCUSSION

DR. PAUL C. BUCY: I wish to ask Dr. Solomon for his explanation of stuttering in left-handed persons who have been trained to use the right hand but who have been relieved from stuttering after amputation of the right arm.

DR. D. M. OLKON: I have had success in correcting stuttering with the aid of the metronome. Briefly, the method consists in adjusting the motor speech to a specific interval set by the metronome. This interval must be consistent with slowness and yet fast enough for good speech. The speed is maintained until the patient becomes "fixed" to the interval, for no other speed in speech is permitted. It is remarkable how quickly the stutterer picks up this motor setting; it serves him as a game, so to speak, in further efforts to correct his speech. Indeed, I have had stutterers of years' standing show marked improvement in three or four months of persistent practice with the metronome.

DR. MEYER SOLOMON: First, as to the explanation for stuttering in left-handed persons who have recovered after removal of the right arm. I do not know of such persons personally; in order to judge, one must know the full facts. If the case were that of a left-handed child who had not been changed to right handedness, it would not be proved that handedness was a factor.

The metronome may be simply a distraction. I said that if the person fixes attention on something that keeps him absorbed he will not stutter. There are many methods of distraction.

As to prognosis: There are many forms of treatment and theories which I have not discussed; results are claimed for all. The prognosis in every case depends largely on how long stuttering has been present and what particular method is used.

STATISTICAL STUDY OF THE ORGANIC FINDINGS IN 129 PATIENTS WITH SCHIZOPHRENIA. DR. JOSEPH C. RHEINGOLD (by invitation).

The findings recorded for 129 patients with schizophrenia hospitalized in the Illinois Psychiatric Institute between 1931 and 1936 were tabulated. In almost every instance the psychosis was of recent origin, and physical examination and laboratory tests were made within the two weeks following admission. The group consisted of 56 males and 73 females. Asthenic and dysplastic body types predominated.

Sixty-nine per cent of the males were 22.5 pounds (10.2 Kg.) underweight, which is 13.8 per cent of prediction. Eighty-one per cent of the females were 22.5 pounds underweight, which is 16.4 per cent of prediction. The mean of the minimal rates of oxygen consumption for the males was 84.3 per cent, and that for the females, 83.3 per cent. In 53 per cent of the males the basal metabolic rate was below —10, and the mean deviation was —22.5. In 69 per cent of the females the rate fell below —10, with a mean deviation of —21.2. Only 1 patient gave a rate above +10, namely, +11. The mean pulse rates were within the normal range. The mean blood pressure for the males was 115 systolic and 76 diastolic, and that for the females, 105 systolic and 72 diastolic. The mean nonprotein nitrogen and dextrose values for the blood were within normal limits. The average cholesterol value for whole blood for the males was 194.8 mg., and that for the females, 218.7 mg. per hundred cubic centimeters (normal range from 150 to 200 mg.). The carbon dioxide combining power of the venous blood plasma was 56.4 for the males and 53.9 for the females (normal range, from 55 to 75). The males gave the following average values for the morphologic blood picture: hemoglobin 86.8 per cent, erythrocytes 4,860,000, color index 0.891, leukocytes 8,010, and neutrophils 61.2 per cent. For the females the average values were: hemoglobin 77.4 per cent, erythrocytes 4,370,000, color index 0.87, leukocytes 7,850, and neutrophils 59.9 per cent. As controls, the results for normal persons examined in the clinical laboratory of the Illinois Research and Educational Hospitals from 1925 to 1937 were used. All the functions reported on showed high variability.

The group of schizophrenic patients appears, therefore, to be characterized by the following organic findings: subnormal weight; reduction in oxygen consumption; normal pulse rate; reduction in the systolic, diastolic and pulse pressures; normal nonprotein nitrogen and dextrose values for the blood; high normal or slightly elevated values for the cholesterol content of whole blood; low normal carbon dioxide combining power; mild secondary anemia, and a normal leukocyte count, with a tendency to relative lymphocytosis. Collectively, the findings suggest hypometabolism. It will be noted that when the values deviate from normal averages, the females show the more marked degree of hypometabolism. Clinical signs of schizophrenia, depression of the specific dynamic action of food, low heat production in response to cold, reduced volume of the lungs, abnormally slow circulation time, decreased blood volume and delayed emptying time of the colon are findings reported in patients with schizophrenia that belong in the same category.

The question arose as to the role of thyroid failure as a possible factor in the production of this hypometabolic state. In a comparison of schizophrenia and hypothyroidism, the newer concept of hypothyroidism, as developed by Lawrence, Rowe, Warfield, McLester, McKean and others, was kept in mind. Data of interest in this connection were found in the social histories, and arrangement of the physical complaints in the order of frequency revealed the common symptoms of hypothyroidism in the first 10 patients of the series. There was an incidence of enlargement of the thyroid of 28 per cent, which is probably of no significance in a goiter region. Eleven patients showed exophthalmos. The other findings were those usually observed in patients with schizophrenia. If a table

of signs and symptoms reported by various authors in connection with schizophrenia and hypothyroidism, respectively, is constructed, a striking similarity is revealed.

The laboratory data reported here were compared with those reported for a group of 126 patients with uncomplicated hypothyroidism studied by Lawrence and Rowe in the Robert Dawson Evans Memorial, in Boston. In this group, 36 per cent of the patients were underweight, the degree of underweight being 14 per cent of prediction. All the patients gave a basal metabolic rate below —10, the average deviation being —24. The mean pulse rate for the group was 66; the blood pressure, 114 systolic and 71 diastolic; the nonprotein nitrogen content, 31 mg.; the dextrose content, 96 mg.; hemoglobin, 87 per cent; erythrocytes, 4,840,000; color index, 0.9; leukocytes, 7,500, and neutrophils, 56 per cent. The concentration of cholesterol in the blood and the carbon dioxide combining power were not studied. It is well known that hypothyroidism is associated with hypercholesterolemia, and Dr. Samuel Soskin has found a tendency to reduction in carbon dioxide combining power in experimental animals with hypothyroidism (personal communication).

Comparison was next made of the findings for the present group of patients and those for schizophrenic patients reported on by Dr. R. G. Hoskins and his colleagues, at the Worcester State Hospital, and by Dr. E. F. Bowman, at the Boston Psychopathic Hospital. In general, except for the pulse rate and blood pressure (which were determined under special conditions at the Worcester State Hospital), the findings for the Illinois group depart from those for the Massachusetts groups in the direction of greater hypometabolism. At Worcester, 56 per cent of the patients gave metabolic rates below —10; the cholesterol content of the blood was 158 mg., and the morphologic picture of the blood was normal. (It should be noted that the Worcester patients were males exclusively.)

The material was reviewed finally for the number of patients for whom the diagnosis of hypothyroidism could be made. The data were studied by a pathologist, the director of clinical laboratories and an endocrinologist; it was agreed that the diagnosis was probable in about 22 per cent of the patients, and doubtful (because of inadequate, not discordant, data) in about 18 per cent. In a group of 138 male schizophrenic patients Hoskins found an incidence of thyroid deficiency of 13.8 per cent.

On the basis of this analysis, the opinion is ventured that thyroid deficiency plays a role in producing the characteristic clinical and chemical picture of schizophrenia. Because of iodine deficiency in the region of the Great Lakes, persons in this area may be more vulnerable to schizophrenia; the psychosis shows a more striking picture of thyroid failure than the disease in patients resident in a nongoiter section of the country. Thyroid failure may be interpreted as part of a total neuroendocrine failure resulting from the collapse of homeostasis in persons with potentially defective substrates who have been exposed to undue demands on the autonomic nervous system.

DISCUSSION

Dr. Alfred P. Solomon: In clinical usage, the term hypothyroidism is associated with dryness of the hands. My studies on the galvanic skin reflex in a group of patients similar to that which Dr. Rheingold describes did not reveal a dry palm in any except those with greatly withdrawn states comparable to sleep. On the contrary, the patients showed low resistance of the skin, a profusely sweating palm.

My opinion is that the low basal metabolic rates in the patients reported on by Dr. Rheingold are comparable with those observed in psychoneurotic persons with chronic anxiety. I have thought of these rates as indicative of exhaustion of the sympathetic nervous system rather than of primary hypothyroidism.

Dr. David Slight: In commenting on these findings in schizophrenic patients, Dr. Rheingold mentioned the tendency to an increase in the cholestreol content of the blood and the low basal metabolic rate. I believe that one also sees these

features in the so-called exhaustive states and in the depressive states. I should like to ask if Dr. Rheingold has made comparisons with findings in patients with depressive states.

DR. JOSEPH C. RHEINGOLD: My intention in making this report was merely to point out what seems to me a striking similarity between the organic findings in patients with schizophrenia and in those with hypothyroidism. All that one may reasonably conclude is that thyroid failure is involved in the schizophrenic psychosis. Whether the endocrine deficiency precedes, follows or merely accompanies the psychosis is an open question. I make the assumption that thyroid failure is part of a general picture of neuroendocrine exhaustion consequent to overstimulation and that the change in behavior attending it depends on the specific vulnerability of the patient. It would be interesting to make a similar study of manic-depressive and neurasthenic patients to evaluate the thyroid factors.

As to the presence of moist hands: It is true that most patients with schizophrenia show clammy skin. There is not a point to point correspondence between schizophrenia and hypothyroidism, but there occurs, it seems to me, in a high percentage of cases a noteworthy concordance of the physical and laboratory findings and a condition in which the diagnosis of thyroid deficiency is warranted.

MEYER SOLOMON, M.D., *President, in the Chair*

Regular Meeting, Feb. 17, 1938

HODGKIN'S DISEASE OF THE SPINE, WITH PARAPLEGIA COMPLICATED BY PREGNANCY. DR. HAROLD C. VORIS and DR. M. H. DRESNER.

Craver and Copeland found that in 27 (15.7 per cent) of 172 cases of Hodgkin's disease the osseous skeleton was involved and that in 16 of the 27 cases (9.3 per cent of the total number) there was vertebral involvement, most often in the lumbar region. In 7 of the 16 cases there were signs of compression of the cord; the records were inadequate in 4 other cases.

Weil reported 46 cases of involvement of the spinal cord associated with Hodgkin's disease. He cited records from the Montefiore Hospital, New York, and the Cook County Hospital, Chicago, to the effect that in 14 per cent of cases of Hodgkin's disease there was involvement of the spinal cord. He divided the cases into those of: (1) lymphogranulomatosis of the epidural space or vertebrae (85 per cent); (2) paraplegia, in which roentgen treatment was given and lymphogranulomatous scar tissue was observed at autopsy (7 per cent); (3) infectious myelitis (4 per cent), and (4) syringomyelia (4 per cent). He observed that the dorsal segments of the spinal cord were involved in 80 per cent of cases, the cervical segments in 16 per cent and the lumbosacral segments in 4 per cent.

REPORT OF A CASE

Clinical History.—A Negress aged 29, in the eighth month of pregnancy, was admitted to the obstetric service of Dr. James Fitzgerald at the Cook County Hospital on Dec. 5, 1937. The diagnosis on admission was polyneuritis associated with pregnancy. The patient had been well until three weeks before admission, when she began to have numbness in the left foot. The following day she had a similar sensation in the right foot. Within two weeks the numbness had progressed upward to the level of the xiphoid process. A week after onset of the paresthesia she noticed weakness of the lower extremities, and within ten days there was complete loss of motor power in the lower limbs. Two days after admission control of the bladder and rectum was lost.

Examination.—General physical examination on admission did not reveal any abnormal findings except enlargement of the uterus compatible with a pregnancy

of eight months. Neurologic examination showed complete motor paralysis of the lower extremities, with flaccidity. The deep reflexes were active in the right lower extremity and diminished in the left. There were Gordon and Chaddock signs and a suggestion of a Babinski sign on the right, with unsustained ankle clonus. No pathologic reflexes were elicited on the left. The abdominal reflexes were not obtained, and Beevor's sign was not elicited. Sensation to pinprick and light touch were absent below the knees. Pain on deep pressure was absent in both achilles tendons, but was perceived in the right calf, where reflex movements of the lower extremities were produced.

Spinal puncture revealed clear fluid, with an initial pressure of 150 mm. Compression of the jugular vein bilaterally caused no rise in pressure, but there was a slow rise with abdominal compression. There were no cells; the Pandy reaction was strongly positive, and the total protein content was 1,250 mg. per hundred cubic centimeters of fluid. The Kahn and Wassermann reactions were negative.

Roentgenograms of the chest were reported to be normal; those of the spine revealed diffuse sclerosis of the body of the first lumbar vertebra, without alteration in contour, and suggested Hodgkin's disease. One of us (H. C. V.) expressed the opinion that there was also sclerosis of the spines and laminas of the fifth, sixth and seventh thoracic vertebrae.

A neurologist who was called in consultation made a tentative diagnosis (before the roentgenograms were taken) of syphilitic meningomyelitis or extradural tumor and suggested consultation with a neurosurgeon.

One of us (H. C. V.) saw the patient in consultation and advised immediate termination of the pregnancy, as the clinical picture was that of a lesion of the spinal cord at the level of the eighth thoracic segment with complete subarachnoid block; laminectomy was urgently indicated. It was recognized that the prognosis for recovery was increasingly poor with each day's duration of the paralysis.

Course.—Attempts at medical induction of labor failed, and the pregnancy was terminated by cesarean section on December 30. Eleven days later, with avertin anesthesia and local infiltration with 0.5 per cent procaine hydrochloride, laminectomy was performed, with removal of the spines and laminas of from the fourth to the seventh thoracic vertebra, inclusive. A firm, relatively avascular tumor was present in the spinal epidural space, extending between the laminas into the erector spinae muscles. After removal of the epidural portion of the tumor the dura pulsated freely. Microscopic sections of the tissue removed revealed Hodgkin's lymphogranuloma.

Convalescence was uneventful; the wound healed by primary intention. Ten days after operation there was still flaccid paraplegia of the lower extremities, with areflexia, loss of position and vibratory sense below the groin and loss of pain sensation below the xiphoid process on the right and below the third lumbar segment on the left, with diminished pain sensation below the xiphoid process on this side. Spinal puncture on that date revealed clear fluid, with no subarachnoid block and 720 mg. of total protein per hundred cubic centimeters of fluid.

High voltage roentgen therapy is being administered at present.

Comment.—This case is presented for the following reasons: (1) the association of advanced pregnancy with compression of the spinal cord and paraplegia; (2) the failure of repeated attempts at medical induction of labor in a case of compression of the cord; (3) a correct roentgenographic diagnosis, before operation, and (4) the addition of another case of Hodgkin's disease of the spine associated with paraplegia to those already reported.

DISCUSSION

DR. PERCIVAL BAILEY: I do not see how one could make a diagnosis of Hodgkin's disease merely because there was one "ivory" vertebra.

DR. VICTOR E. GONDA: I saw the patient lately; I am afraid that she now has not only a localized tumor, described as the only lesion at the time of the

operation, but infiltration of the lumbosacral segments. I am afraid that this is the cause of the flaccid paralysis of the lower extremities.

DR. HAROLD C. VORIS: It should be emphasized that the roentgenologist made the diagnosis of Hodgkin's disease. I could not see how he was able to do so and did not consider it seriously because it was made with reference to the first lumbar vertebra while the neurologic level of the lesion was at the eighth dorsal segment (sixth dorsal vertebra). At operation the tumor was observed to have extended into the erector spinae muscles. The mass was firm and granular and presented the appearance of carcinomatous tissue. It was with surprise, therefore, that I received from the pathologist a report of Hodgkin's granuloma.

DR. SIGMUND KROMHOLZ: This case is of interest from the standpoint of extension of the disease. Prior to the operation the patient presented atypical spastic paraplegia, which indicated that the lesion was located at the level of the thoracic segments. Now, only a few weeks after the operation, the paralysis has changed to a flaccid type, with loss of the deep reflexes. It appears, therefore, that the lesion has extended downward to the level of the lumbosacral enlargement and that the disease is progressing rapidly.

DR. M. H. DRESNER: In answer to Dr. Bailey: Dr. M. J. Hubeny, of the roentgenologic department, mentioned Hodgkin's disease as the first diagnosis because there was no alteration in contour of the affected vertebra. However, he also considered that a metastatic malignant growth was possible. It has been believed throughout that there was not only compression high in the cord, as evidenced by the sensory level at the xiphoid process, but infiltration in the lumbar segments of the cord, as indicated by vertebral involvement.

EMOTIONAL FACTORS IN HYPERTENSION. DR. KARL A. MENNINGER, Topeka, Kan.

This article appeared in full in the April 1938 issue of the *Bulletin of the New York Academy of Medicine.*

A point of view which attempts to correlate the psychologic, physical and chemical findings in disease is presented, with some psychologic data concerning hypertension. Most patients are examined physically and chemically but not psychologically, whereas proper investigation would probably lead to recognition of special psychologic factors in every disease. In the study of hypertension, investigation of the psychologic features of the condition is the more readily made because of the parallelism between fluctuations of the blood pressure and those of the emotions. The emotional fluctuations should be regarded not as the cause or the effect but as a concomitant of the hypertension. The following findings impress those who have made psychologic examinations of hypertensive patients: 1. Transient hypertension may be induced in persons by emotional stimulation. 2. Some patients show gross pathologic disturbance of the emotional status or reaction. 3. Chronic hypertension may sometimes be reduced by various methods which are essentially psychologic.

Psychologic studies have been made both of the conscious and of the unconscious emotional factors in hypertension; the conclusions indicate that hypertensive patients are characterized by external poise, often gentleness and amiability, beneath which there exists a strong undercurrent of fear arising from strongly repressed aggressions, usually dependent on resentment over threats to the patient's overdependent security. Hypertension, therefore, may be expected in a patient whose early childhood has been threatened by poverty, death or other disaster whereby he was forced into premature self reliance, which later showed itself in the form of more or less material success accompanied by constant internal anxiety.

The therapeutic effect of psychologic technics in treatment of hypertension is indicated by several reports in the literature. The concept of primary constructive and destructive tendencies is suggested as the coordinating determinant behind the various aspects of a disease manifesting itself in physical, chemical and psychologic phenomena.

DISCUSSION

DR. LOUIS LEITER: I admire Dr. Menninger's honesty in concluding that many more observations are needed and that the facts obtained must be correlated from many different aspects. Perhaps I believe more in physical first causes than he does. There is evidence that hypertension may be produced in animals by clamping the renal artery. Clinicians and pathologists have carried this principle further. They believe that there are many intimal clamps in the renal arterioles of human beings with an early stage of hypertension. Of course, the patient with hypertension is subject as a personality to the same reactions as the normal person, but it remains to be demonstrated that repressed rage is the underlying cause of chronic hypertension.

Dr. Menninger's paper should stimulate the collection of sufficient data for the establishment of a relation between chronic hypertension and emotional conflicts. To be of significance the study must include preliminary medical observations lasting over a period of years, followed by thorough psychologic analysis and further medical observations during a period of years when the patient is readjusting himself. Under these conditions one may be able to learn whether the hypertensive process can really be reversed. This may seem to be a formidable program, but it is worth while in view of the enormous prevalence of hypertensive disease in persons in the older age groups. The present psychiatric or psychoanalytic investigation of hypertension is so scattered and involves so few patients, under such varying medical control before and after psychotherapy, as to justify the employment of a radically different procedure if one is to approach a solution of the problem in any reasonable period.

DR. FRANZ ALEXANDER: I have little to add to the masterly presentation by Dr. Menninger so far as psychologic observations are concerned. I can corroborate his conclusion that there is a psychologic state typical of hypertensive patients. These persons show certain psychologic charateristics, as do those with peptic ulcer. There is ample evidence that there is a hereditary factor, possibly a constitutional vasomotor lability. This specific constitutional factor may manifest itself also in certain psychologic features. However, there are indications that these psychologic factors may have an etiologic significance in the production of essential hypertension.

I have observed that the psychologic state most typical of hypertensive persons is the presence of strong hostile, aggressive impulses which the patient can neither express freely nor repress deeply. These patients give the impression of a volcano which is ready to erupt, but never does. Comparison of the clinical findings concerning the accumulated hostile impulses with Cannon's experiments on rage in animals makes plausible certain conclusions. Cannon demonstrated that under the influence of rage and fear a physiologic condition develops which is useful for the animal in fighting an enemy or fleeing from danger. Increased blood pressure belongs to the complex physiologic syndrome following rage and fear. The blood is pressed out of the splanchnic area, and its flow to the brain, lungs ad muscles is increased. At the same time, the adrenal system is stimulated, and the speed of coagulation of the blood is increased.

An increase in the blood pressure as a reaction to acute anger is common in normal persons. The vasomotor system of persons who are chronically under the influence of inhibited anger is subject to permanent psychologic stimulation. In other words, in persons who during daily life easily become emotionally aroused but can never give free expression to hostile impulses the vasomotor apparatus is frequently, if not continually, exposed to such psychogenic stimulation. In animal life the rage process has a typical course. The animal which is exposed to danger becomes enraged, attacks the enemy and fights it or flees from it; a period of exhaustion follows, and the blood pressure returns to normal. In civilized life this rage process seldom comes to such complete consummation. In competitive civilization there is always latent hostility among people. They must fight each other and at the same time continually control the hostile impulses and cooperate

with others. Soma Weiss and other clinicians have shown that persons with essential hypertension are, in a high percentage of cases, typically neurotic. Therefore, one may assume that such irritable psychoneurotic persons, who cannot handle aggressive impulses as well as normal persons and are less adjusted to the conditions of civilization, are to a greater extent than normal persons exposed to constant, or often recurring, psychogenic stimulation of the vasomotor apparatus.

Many clinicians, to mention only Fishberg and Fahrenkamp, describe two phases in the development of essential hypertension: (1) a period of fluctuation and (2) a malignant phase in which the blood pressure remains constantly on a high level. If this is true, one may assume that in the fluctuating phase psychologic factors may play an important etiologic role. If continued overstimulation of the vasomotor system persists for years, this functional overtaxation may lead to certain degenerative processes in the vessels, which are responsible for the malignant form of hypertension. It may well be that the local ischemia of the kidneys to which Dr. Leiter has referred may develop as the result of such a psychogenic functional disturbance of long duration.

I submit all this as a plausible working hypothesis to explain the typical clinical course of events leading to hypertension. This working hypothesis goes a step beyond the usual etiologic concept, which tries to explain the disturbance of function resulting from tissue changes in accordance with the classic concepts of Virchow. One's thinking concerning etiologic factors should not stop here. What is the cause of the pathologic changes in the tissues? Even if Goldblatt's observation regarding the significance of the local ischemia in the kidneys is correct and one finds that vascular changes are responsible for the ischemia, the deficiency should be considered only as an immediate factor and not as a final etiologic explanation. What causes the local ischemia? I submit the working hypothesis that it may be the end result of a functional disturbance caused by chronic emotional stimuli.

To summarize: If this hypothesis of the etiologic factors is correct, essential hypertension is the reaction of especially sensitive neurotic persons to the complexities of civilized life, in which they are exposed to fear, aggressions and angers which they cannot successfully control. They may control them outwardly even more than others, but the vegetative functions are disturbed by the permanent influence of the excessive and pent-up aggressive impulses. In this connection, it is noteworthy that Schwab and Schultze found that the Negroes of North America supply a high percentage of cases of malignant hypertension while the Negroes of Africa seldom have hypertension. It seems as though the young race has greater difficulties in adjusting itself to the conditions of this civilization, which stimulates so many competitive feelings of aggression and at the same time requires control of these tendencies to such a high degree.

Dr. Alfred P. Solomon: Dr. Menninger spoke of the difficulties in securing accurate records of variations in blood pressure during an interview. He emphasized the value of such a record in determining the meaning of interrupted readings. Dr. Alexander spoke in detail of the reaction in blood pressure and suggested that chronic hypertension is the result of long continued fluctuation of stimuli. Dr. Chester Darrow has perfected an apparatus which he and I are using at the University of Illinois College of Medicine; it provides accurate continuous photographic records of systolic and diastolic pressure. With this apparatus we showed that in psychotic persons when psychologic resistance to the interviewer is present or anger or rage exists for other reasons there are marked upward fluctuations of blood pressure in response to crucial ideational stimuli. We have shown further that when these patients are successfully treated with insulin or metrazol the fluctuations disappear, with a resulting change in attitude.

We found a person who appeared to be timid and reticent; yet his blood pressure indicated that internally he was very hostile. Study of his personality confirmed this observation.

I believe that studies on reactions of the blood pressure will add much to data secured only by recording the level of the blood pressure.

DR. KARL A. MENNINGER: I feel a pang of remorse that I neglected to mention the stimulating work that I know Dr. Solomon and Dr. Darrow are carrying on. I saw it and was delighted with it; I envy them the instrument they have perfected. That confirms what I said at the beginning of my talk—that Chicago has led the way in this field—and I hope it will continue to do so.

As to what Dr. Leiter said about the work of Dr. Harry, at Cleveland, and also as to Dr. Alexander's theory of Cannon's work: I do not have the same compulsion to explain the mechanisms of these reactions. I do not feel it is necessary even to try to do so. I believe that these steps must be filled in by other workers. Some of my physiologist friends tell me that Cannon's theory is not airtight; I believe that it is not wise to base an entire new hypothesis on it. I think that one should investigate the aspects of the problem empirically. With regard to the idea of organic self destruction which I outlined a year and a half ago before this society (The Psychologic Aspect of Psychogenic Somatic Disease, ARCH. NEUROL. & PSYCHIAT. **37**:1384 [Dec.] 1936): It was my wish to speak more elaborately tonight with respect to just one symptom of this destructive tendency. One must fill in the gaps slowly. If I am more radical in general theory than Dr. Leiter and Dr. Alexander, I am more conservative in particular explanations.

TREATMENT OF MYOTONIA CONGENITA WITH QUININE: REPORT OF A CASE. DR. HARRY A. PASKIND and (by invitation) DR. ROBERT C. LONERGAN, Evanston, Ill.

ACTIVATION OF MECHANISMS FOR HEAT LOSS BY LOCAL HEATING OF THE BRAIN. DR. H. W. MAGOUN (by invitation).

Local heating of the brain of the cat with a low voltage, high frequency current passing between electrodes oriented with the Horsley-Clarke apparatus has demonstrated a reactive region which responds to an elevation of temperature by initiation of activities leading to heat loss, with marked acceleration of respiration, panting and the appearance of sweat on the foot pads.

The reactive elements appear to be concentrated in the mediocaudal part of the ventral portion of the telencephalon and, in lesser concentration, are continued backward through the diencephalon, as far as the anterior end of the midbrain. In the telencephalon, the responsive region occupies a position between the anterior commissure and the base of the brain. In the diencephalon, it is located in the hypothalamus and the ventral part of the thalamus, and it occupies a progressively more dorsal position at more caudal levels. At the anterior end of the midbrain it is located in the vicinity of the central gray matter around the aqueduct.

The results are interpreted as indicating that in the normal animal the reactive region contains structures which are activated by the rising temperature of the blood and lead to activities resulting in heat loss.

DISCUSSION

DR. R. M. STRONG: There is a similar center for heat regulation in birds and reptiles. In birds it occurs in the dorsorostral region of the midbrain. Heating this center raises the respiratory rate in the dove to 600 per minute. This astonishing rate is not surprising, however, when one considers that the respiratory rate rises normally in birds during flight to an exceedingly rapid rate. The rate is correlated with the wing strokes. In the dove the respiratory rate rises in flight to over fourteen times the frequency at rest.

DR. R. P. MACKAY: I wish to ask Dr. Magoun to what extent he believes these results may be applied to man. A priori, one might doubt that the heat-regulating center in cats is in exactly the same location as that in man. The regulation of body temperature in man consists chiefly in sweating and peripheral vascular dilatation, and only secondarily in the dissipation of heat by increased respiration, while in cats respiratory increase is far more important. Perhaps in these experiments Dr. Magoun is stimulating the respiratory mechanism rather

than a heat-dissipating center, and a similar anatomic location in the human hypothalamus might be found to control only a fractional and unimportant part of the so-called heat-regulating mechanism.

DR. JULES MASSERMAN: I can add only one observation relevant to Dr. Magoun's excellent demonstration. In unanesthetized cats prepared as recovery animals, the injection of minute amounts of strychnine directly into the anterior portion of the hypothalamus will also produce panting without any marked change in the body temperature, which may indicate that the drug facilitates the activity of a local neural mechanism concerned with the regulation of heat.

DR. H. W. MAGOUN: I am glad that Dr. Mackay has raised the question of the relation of these results to man, for, as he said, the mechanisms of heat loss are different in the cat and in man. The monkey resembles man rather than the cat in that it is dependent more on increased sweating than on increased respiration for the elimination of excessive body heat. We have not repeated these experiments on heating the brain with the monkey, but we are fortunate in having the report of Ranson, Fisher and Ingram (Hypothalamic Regulation of Temperature in the Monkey, ARCH. NEUROL. & PSYCHIAT. **38**:445 [Sept.] 1937). They have shown that monkeys with lesions in the anterior part of the hypothalamus, in the region found in the present experiments to respond to elevation of temperature by initiation of activities resulting in heat loss, fail to respond by sweating when placed in a warm environment, the body temperature rising to dangerous levels as a result of inability to defend themselves against overheating. Thus, it appears that even though the primates employ a different means of eliminating body heat, the function is controlled by the same region of the brain as that in the cat.

I am not as familiar as are many clinicians with the results in man, but I may mention the case reported by Davison and Selby (Hypothermia in Cases of Hypothalamic Lesions, ARCH. NEUROL. & PSYCHIAT. **33**:570 [March] 1935) in which an angioma invaded the base of the diencephalon and destroyed the preoptic region and the hypothalamus. No detailed study of regulation against overheating was made, but it was noted that the patient failed to sweat even during the hottest summer weather in New York. Any one who has spent a summer in New York will, I think, agree that this is evidence of impairment in heat loss activity.

The postoperative hyperthermias which in man sometimes follow operative intervention at the base of the diencephalon are characterized by suppression of all heat loss activities; they also indicate the importance of this region in regulation against overheating.

I am pleased to hear the corroborative evidence obtained by Dr. Masserman with a different experimental technic.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

IRVING H. PARDEE, M.D., *Chairman, Presiding*

Regular Meeting, Feb. 8, 1938

THE DRAMA AS A THERAPEUTIC MEASURE IN THE TREATMENT OF ADOLESCENT BEHAVIOR PROBLEMS. DR. FRANK J. CURRAN.

This paper describes a form of group treatment of adolescent behavior problems in boys from 12 to 16 years of age at the psychiatric clinic of the Bellevue Hospital. The children write, produce and act in their own plays. The subject matter is left to the discretion of the children, but the majority of the plays deal with problems of aggressiveness or are concerned with situations at school, the hos-

pital or the home. Attempts are made to correlate the patients' emotional problems with the types of drama produced. After the play, group discussions are held with all the children in the ward; by this means they are able freely and spontaneously to discuss various problems of aggressiveness, etc.

This technic not only is of help in diagnosing and treating the behavior problems of many children at one time but adds material which individual psychotherapeutic conferences might not bring out. The point is stressed that this method is not a means of occupying children or giving them superficial amusement but a form of group catharsis by play acting.

DISCUSSION

DR. JACOB L. MORENO (by invitation): The material which Dr. Curran has presented speaks for itself. In the last few years the drama as a means of psychotherapy has gained momentum; it may be interesting to picture that two Greek philosophers, Hippocrates, who developed the art of healing, and Aristotle, who initiated the art of catharsis, have here a marriage. Psychiatry has often acted as a marriage maker, bringing into medicine relations which have not been visualized before. I wish to emphasize only one point which Dr. Curran mentioned: the process of catharsis. I have had experience with similar material during many years of work. The process is incorporated in the form of a drama, with a number of persons cooperating in presenting an idea and warming up to various roles, which may in the past have had psychologic significance for them. I make only one point of criticism. In the first years of our work, which started in Vienna and later was carried on in the United States, my colleagues and I allowed the boys and girls to write plays and to act them out. However, for various reasons, we concluded that they should not be allowed to write their plays but should express and develop spontaneously the roles as they went along. It seemed to us that this gave a greater possibility of expressing the particular difficulties the patient had. I should like to hear what Dr. Curran says with regard to that problem; he may have some ideas. It seems to me the crucial point in the use of the drama in psychotherapy. If the process of catharsis is "used up," so to speak, in the writing of the play, it will be exhausted before the play is acted. When the patient acts out a part or expresses it spontaneously without predetermination, one has greater possibilities of learning from observation. In fact, one takes the patient by surprise. For instance, if the patient chooses a certain role to play, he may not do anything for a minute or two. Perhaps the immediate result is not as effective as it otherwise would be, but in the end it will be much more so. However, to return to Dr. Curran's paper: In the end the same fundamental problems exist: the spontaneous relation of the subject to the role he has chosen and the opportunity he has to work it out with other persons whom he has chosen as partners.

DR. JOHN LEVY: All who are working in the field of children's behavior problems, especially in the clinic, owe a debt to the work in group therapy that Drs. Curran, Schilder and Bender are doing at the Bellevue Hospital. Those who have a chance to compare the opportunities for treatment in private practice with those in clinical practice may admit that the patient in the clinic—the child at least—suffers considerably and faces a real deficit in treatment. Because of the large number of patients in the clinic, it is not possible to give them the benefits of psychotherapy that the private patient secures. I think that the patient should be seen at least three hours a week in order to gain any real benefit from therapy; no clinic can give this amount of time to the large group of patients it must handle. I hope that through the group work at the Bellevue Hospital efforts for the clinical patient will be as successful as for the private patient. Dr. Curran points out that he is able to combine his group approach with individual therapy. This, it seems to me, is of tremendous value. By seeing the child in various types of social relations he is able quickly to obtain findings which on a

strictly individual basis would take a long time to secure. These findings are immensely helpful in working with the children individually. It is similar to the situation in psychologic testing in which in group tests the psychologist is able to pick out individual differences which he can put to use in individual follow-up work. I am hopeful that this pioneer work in group therapy will help to overcome the deficit from which the clinic child suffers.

My next point concerns the relation between the expression of aggression on the part of the children and the therapeutic results. In the group with which Dr. Curran is dealing such expression does not seem particularly important. The children come from a background in which aggression is all too readily expressed. In his material the amount of sadistic feeling elicited by superficial contact was overwhelming. With private patients the problem of aiding children to express aggression is important because such children come from a different social level—from a background where aggression is taboo, where they must be well behaved. The problem in the group described tonight is rather one of inducing the children to express affection. In this connection, it is interesting to note that whatever love feelings were elicited had to be apologized for and suppressed. "Butch" or Tony, who were so hostile, might as well have been talking on the street; but Percy, who was tender, was "in a jam" in the hospital group. He had to express his tenderness in the face of all the social opposition. Interestingly, this is true of private patients who are starved for affection. They, too, have trouble in expressing tenderness. For most private patients, however, the real problem is one of encouraging the expression of hostility. For them hostility is as difficult to express as tenderness is for the clinical group. In such cases I use the same technic that Dr. Curran applies in his group.

In other words, the difference in social levels seems to make a real difference in the way in which the problem of expressing one's feelings manifests itself. The fundamental problem is, of course, the same. Whether one is dealing with groups in the clinic or with groups of private patients, one finds the same situation: All the patients are afraid of certain feelings. The social level seems to determine what feelings bother them. In a milieu in which aggression is the order of the day—in which fighting, yelling and squabbling are part of the daily routine—the children have no difficulty with hate feelings. Love feelings must be kept in the background. Any boy who shows tenderness, affection or gentleness is a social outcast. He is too soft. He must be a "tough guy" to be acceptable. He fights any love impulses he may feel, and becomes tremendously afraid of them. The child from a gentler environment fights his hate feelings and is terrified when, in one way or another, they come out in spite of himself. Whereas the children in the clinical group encounter trouble by being too "tough," the children in the private groups encounter trouble by not being "tough" enough. Naturally, there are variations on this theme, with limitless differences in environmental forces. It seems to me, however, that one must recognize the relation between the social milieu from which the child comes and the form in which his behavior problems manifest themselves. I think that it is particularly important with Dr. Curran's group. They are boys whose too great, not too little, aggressiveness has caused trouble.

Another point in connection with the expression of aggression may be mentioned. One finds that as the children in any group express their aggression they also express a great deal of esthetic feeling. I imagine that with Dr. Curran's group this esthetic feeling would come with the expression of more tender feelings. These children would be just as afraid of writing a play which consisted of poetic feelings as the privileged group would be of writing a drama about murder. When, however, the first group became emancipated from aggression, they might even write poetry.

I have a group of children at the clinic of mixed social levels. They are divided into two groups: the "aggressive" and the "nonaggressive" types. These two groups are given an opportunity to play together in a room in which there is

a great deal of art material for use. There is also a competent instructor who, on the one hand, may assist them in developing whatever artistic impulses they have and, on the other, may be a gang leader who helps them to express their aggressive feelings. The interesting point is that the "aggressive" children do not remain so indefinitely. They have an opportunity to express first their aggression and later on their tenderness. With the development of tenderness a great deal of esthetic feeling is expressed in art forms. They show their tenderness through their art. A gangster ends by painting delicate flowers. The "nonaggressive" children begin by writing and painting more delicately. Eventually, they turn to roughhousing before returning to art. In other words, this group shows a real relation between aggression, tenderness and art. I believe the same would be true in the drmatic activities of the group described by Dr. Curran.

I am looking forward to the paper in which Dr. Curran will tell, I hope, of the individual contacts he makes with the members of his group. I place a great deal of stress on these contacts and on the kind of relation he will establish with each child. Being particularly interested in individual therapy, I look forward to seeing how the more personal relationships evolve from the group relationships and what roles he has to play as therapeutist.

In this connection, I wish to refer to Dr. Curran's comment on insight. I think he places too much stress on the development of insight. Insight, it seems to me, should be considered as secondary to the relationship which is established with each child. For me, the relationship, and not the insight, is therapeutic. Insight, I believe, can develop only after one has satisfied these primary emotional relationships.

Dr. Thomas K. Davis: All must know that many a young physician does not choose pediatrics because he looks ahead and sees that he will be handicapped by the inability of the child to give his own anamnesis. It is no doubt true that many a psychiatrist in the past, and even now, does not take up child psychology because he thinks he will be similarly handicapped. Therefore one must be grateful to the group at the Bellevue Hospital for their new methods in working with children, and now to Dr. Curran for his excellent paper on the modified use of the drama. The method has been carried out somewhat differently before; I appreciate the initiative shown in the new technic. In reading the paper, I was struck by the fact that one can hardly gather the gist of it without doing the work one's self. Dr. Curran read his paper with such dramatic effectiveness and clarity that much less waste motion was in evidence than appeared from reading it in manuscript.

As regards the conclusions, I agree with all of them. I picked out as one of the telling sentences this statement: "For the first time they learn that they are not solitary sinners, but have feelings and temptations which the majority of human beings have." My picking out that sentence places me in opposition to Dr. Levy's point of view that insight is not essential. Let me say one thing further. This procedure strikes me as a swing toward Jung. I say that because drama began with religion. Early biblical plays and miracle plays developed together—religion and drama. One cannot go anywhere in drama without dealing with values, ethics and reverence. Therefore, I think that the psychiatrists who are using drama for their studies are moving in the direction of Jung. Speaking of reverence, the psychiatrist's insistence on what one calls reality ignores reverence as a possible factor in the normal psychobiologic makeup. I ask whether psychiatry will broaden its conception of reality.

Dr. Frank J. Curran: In answer to Dr. Moreno's question about having the patients act spontaneously rather than write out the plays: It is my belief that the technic must depend on the number of patients one is working with. When one has 40 or 50 boys who are very aggressive (as they are at the Bellevue Hospital), I do not think that that particular technic would be successful. I have tried it occasionally and found in a few minutes that windows were being broken

and the furniture destroyed. Therefore, the technic which I have described seems to work better with this particular group of boys at the Bellevue clinic.

In reply to Dr. Levy's remark about these children having artistic leanings in other fields: I agree with him. I did not stress that point in this paper. At the Bellevue Hospital my associates and I have not only dramatic productions in the adolescent ward but other types of activities, including art, music and dancing.

Dr. Davis' remark concerning the swing toward Jung is interesting. I do not believe that I am prepared at present to discuss that point in detail.

THE PSYCHOLOGY OF SCHIZOPHRENIA. DR. PAUL SCHILDER.

An attempt is made to formulate a unified theory of the psychologic state in schizophrenia. The schizophrenic patient threatened in early childhood withdraws into more secure positions. He tries to heighten the importance and strength of his personality. Furthermore, he uses primitive methods of defense by immobility or negativism. Catalepsy is, from a psychologic point of view, an attitude of giving in. He may also use the technic of violent attack. He does not dare retain higher forms of object relations. Primitive types of libidinous development occur. In addition, one finds primitive stages in develoment of ego ideals. The primitive attitudes come also into appearance in the formation of language and thought processes. Symbolism, projection and renewed indentifications belong in this sphere. The primitive threat is revived by dangerous situations of everyday life. The threat of being destroyed leads to outbursts of aggressiveness, which appear particularly clearly in children with schizophrenia. Many of these manifestations of primitive motor defense and obedience have close relations to organic mechanisms in the brain. However, the perceptive and motor faculties are disturbed in a sphere which, although organic, is not the same as that involved in cases of gross lesions of the brain.

During and after metrazol or insulin shock, aphasic and confusional states occur, of clearcut organic type. They were studied with the help of the gestalt and the Goodenough tests. The phenomena belong to an order other than do those associated with schizophrenia. After the insulin shock and the metrazol fit, the patient has an increased capacity for transference. It is as though the patient feels that he is safe from a psychologic point of view and that he can form a better relation with the world and can consider the psychotic experience as of no importance. One may speak, with Jelliffe, of the overcoming of a death threat if one keeps in mind that this threat comes from the depth of the organism and is a reflection of the organic occurrence. At any rate, the patient reorganizes his attitudes in connection with the physiologic reorganization. The amnesia does not play an important part in the psychophysiologic reorganization. The patient gains by the treatment objective, but not psychodynamic, insight into the occurrences of the psychosis. He needs, at any rate, psychologic help, although one does not know yet whether this can prevent relapses. Psychologic help does not seem to be essential for the immediate curative effect. Schizophrenia can be understood, at least to some degree, from a psychologic point of view, and one may state that the organic process of schizophrenia is modifiable in some degree by psychologic methods. The organic methods of treatments are even at present more effective.

DISCUSSION

DR. LELAND E. HINSIE: Dr. Schilder's communication represents a continuation of his many efforts to unite psychologic states definitely with tissue structures. He is one of the leaders who advocate that the problems of somatic and psychic unity have been solved in principle and that the remaining work involves the application of these principles to the various expressions, normal and pathologic, of psychologic phenomena. Regardless of the validity of their claims, investigators who are working vigorously to advance understanding of the relation of the soma and the psyche should be encouraged. Many are too timid to try. It is to the credit of Dr. Schilder that his laboratory of investigation is the sickroom.

I think that Dr. Schilder's general theme may point in the right direction. To him, as well as to a number of his predecessors and contemporaries, it seems probable that the schizophrenic patient reproduces his phylogenic as well as his ontogenic development. A great part of the thought, action and feeling of patients with schizophrenia seem, as Jung, Lévy-Bruhl, Storch, Schilder and others have shown, to have a striking resemblance to these faculties as they appear in their primordial setting. Although the facts are not yet as substantial as one would like, there seems to be a recrudescence of primitiveness as a basic problem in schizophrenia. It is true that in the vast majority of persons in whom schizophrenia develops there is failure to advance to mature, adult types of social and personal adaptation and integration.

A feature common to many schizophrenic persons is regression. It is not unusual to encounter patients who have receded through the various levels of their growth. With the onset of morbid symptoms, whatever wholesome attachments the patient had made to the world of reality are gradually relinquished in favor of the world of fantasy; after the abandonment of natural reality, there is loss of heteroerotic interests, with attempted adjustment, on a morbid projection basis, to the next earlier level, homoerotism. The struggle may continue at this level for years, in which case the symptoms are largely those of the paranoid reaction. Often, however, the homoerotic level represents merely a phase through which the patient must pass in his regression. In his further backward movement he reproduces the narcissistic phenomena of his youth to such a degree that he appears to simulate the state of infancy. While he has been undergoing these changes, fantasy has been replacing reality. It is noteworthy, however, that the fantasy is often attached to the world at large; that is, the patient simultaneously abandons natural reality for fantastic reality. In no other illness is the hypercompensatory mechanism so thoroughly developed. The person who cannot adapt himself to a small sector of the natural environment can, through the medium of a psychosis, establish intimacy with the entire universe. Cosmic identity, the role of the redeemer and unrestricted omnipotence, with the many other features that are observed concomitantly, such as bisexuality, complete change of identity, incorporation of multiple personalities, personalization of the viscera and a host of allied changes—all these changes stamp the person as superlatively overcompensatory.

Another fact of great importance has to do with the character of thinking, acting and feeling. There is a law of the mind that in their development, thought and language, change from feeling, concreteness and perception in the direction of reasoning, differentiation and abstraction. Many schizophrenic patients, as Schilder mentions, fall back on the simpler form of mentality.

Primitive mentality, shorn of the niceties of more advanced forms of civilization, possesses a closeness not to the soma but to the soma as a means of expression. "Language" is largely pictorial, perceptual; it is made up to a large extent of images. Moreover, the body enters as a means, par excellence, of communication from one person to another. There are many other features, admirably delineated by a number of investigators, that lead one to believe that among primitive peoples the mind is only vaguely differentiated from the body. Examples could be given to convince one that mental and physical functions are one and the same.

Dr. Schilder's résumé of these observations, brief as it is, carries one back to that relatively undifferentiated and phylogenetically embryonic mind.

I cannot think with Dr. Schilder, however, that schizophrenia "is a primitive reaction based on organic changes in the central nervous system." One cannot be as dogmatic as that with the present knowledge of nerve tissue. It is an attractive speculation, but it cannot comprise the reason for advancing the hypothesis that schizophrenia is an organic psychosis. I think a sounder approach to the subject is to be found in the studies from the school of constitutional anomaly and pathology (di Giovanni, Viola, Pende, Bauer, Benecke and others). Instead of

accepting the statement that "the psychologic attitudes are the reflection of deeper lying physiologic problems," I suggest that Dr. Schilder's opinions would be more in keeping with the facts if they were offered as hypotheses. There is no proof, to quote him further, that the psychologic state of schizophrenia is associated with "the construction and reconstruction process [that] is going on in organic layers."

Nor does my clinical judgment parallel that of Dr. Schilder when he says that "there cannot be any question that the patient at the end of treatment is psychologically not much better adapted than he was before the treatment started." First, Dr. Schilder claims that the symptoms of schizophrenia are made up of psychologic phenomena; second, that the psychologic phenomena are due to organic changes; third, that the organic changes are effectively modified by certain organic methods of treatment, and, fourth, that the psychologic phenomena are little better after than before treatment. In other words, I can only understand Dr. Schilder to say that removal or correction of the cause has no essential influence on the result.

One might say that not much improvement is to be expected when the condition has persisted for years. It does not seem logical, however, to claim that a primary cause of symptoms, irrespective of its duration, may be corrected without producing any basic changes in the symptoms. It is the equivalent of maintaining that a morbid syndrome, based on organic alterations, persists when the organic pathologic process is removed. If a syndrome continues unchanged when an alleged cause is removed, I think one should look elsewhere for the cause. It should be remembered that, Dr. Schilder does not believe that the results are spatially remote from the cause; to him, both cause and effect reside in the same tissues.

I think the primary motive of Dr. Schilder's communication centers in the question of the influence of insulin and metrazol on schizophrenia. It appears to listeners that these agents produce favorable results. In his opening paragraph, Dr. Schilder states that the two forms of treatment have "doubtless practical value." He does not doubt their practical value. Then, on page 17, he claims that "the degree of this efficiency [referring to insulin and metrazol] has yet to be determined." He does not know their values. If Dr. Schilder does not know how efficient a measure is, he cannot justifiably state, as he does, that "the organic methods of treatment are even at present more effective" than the psychologic. The truth is that he is comparing two unknowns, the result of which must also be unknown. Dr. Schilder recognizes that himself when he says that "observations of several years will be necessary" before valid conclusions may be drawn.

DR. A. A. BRILL: I was much impressed by Dr. Schilder's presentation. Dr. Schilder is one of the few who has the capacity to review any subject, no matter how complicated, and to look at it from all angles, and who has the courage to come to definite conclusions about it—a faculty which only few persons possess, particularly with regard to schizophrenia. First, I am not afraid of the word "complex," even if it is too mechanical, as Dr. Schilder puts it. I understand it; I was present when it was worked out; I remember distinctly the fights between Bleuler and Jung concerning the causes of schizophrenia, which Dr. Schilder mentions. Jung, as Dr. Schilder says, considered the disease to be due to a definite organic condition, a toxin. I participated in a number of these discussions, when the question was asked: "Why is it that a person may feel fine, and when his complex is suddenly aroused may immediately lose his appetite, feel badly and act as though he had been poisoned? Is this due originally to the poison, or is the poison produced by the complex?" There were always heated discussions, but one never came to any conclusion. Dr. Schilder presents a thorough review of the literature. He begins with Freud, who called attention to the psychogenetic element in "paranoid dementia," and states that Freud never excluded the organic element and often said that even if a disease is organic one is not excused from explaining the psychogenetic aspects in the case. What I understood Dr. Schilder

to demonstrate is this. He does not agree with Campbell and Meyer, who expressed the belief that schizophrenia is psychogenetic and can readily be explained on the basis of a "banal" conflict. He believes that it goes much deeper when one investigates the problem psychoanalytically. Dr. Schilder claims that when one observes schizophrenic patients in a state of catatonia—their general behavior and their insensibility to pain—it seems that they are reacting to an organic, or rather a toxic, disturbance of the central nervous system. He corroborates this by observations on patients with schizophrenia treated with metrazol and insulin. Dr. Schilder notes that such schizophrenic patients seem to react to the treatment with certain mechanisms that are definitely organic; they behave as if they were intoxicated by a toxin. Dr. Schilder notes that in general their behavior, their perseveration, their mode of transference to the environment and persons immediately after they emerge from the treatments also indicate a certain affect that is more characteristic of the organic than of the psychogenetic syndrome. I fully agree with Dr. Schilder's reasoning. One knows, for instance, that schizophrenic patients who have been markedly indifferent and apathetic for twenty years or more show real affective behavior when they receive a cerebral insult; they react like patients with organic lesions. Dr. Schilder cites Pick and Allers, the Angyals and others, all of whom found perceptual difficulties associated with schizophrenia which resembled the interparietal syndrome. Gurevitch attempted to correlate this syndrome with the symptomatic picture in schizophrenic and toxic psychoses. The gestalt tests of Drs. Bender and Goodenough also point to an organic disturbance in schizophrenia. What Dr. Hinsie said is true; I have no quarrel with his conclusions. In brief, all I can say is that Dr. Schilder's conclusion that the schizophrenic process is organic because it shows certain definite toxic mechanisms seems to be correct. However, I should like to know what happens in cases other than those of schizophrenia in which a toxic reaction is shown for which no organic basis can be discovered. I am thinking of psychic suicide by primitive persons, who, because of a psychic shock, decide they are going to die and then pass into a comatose state and die within a week or so. I have a large material from reliable surgeons and physicians who have examined such persons soon after they decided to die and found nothing organically wrong with them. Nevertheless, they passed into a comatose state and died exactly as they themselves predicted. Autopsy showed nothing of an organic nature. What happens in these cases? One apparently sees here a definite organic mechanism of a toxic nature with a psychic basis, a fear of the medicine man or of a broken taboo.

Dr. Schilder deserves a great deal of credit for having expounded the subject so thoroughly and for giving the best résumé since Jung produced his classic psychologic description of dementia praecox. He discusses all the mechanisms so well developed by Jung and brings them up to date. Dr. Schilder's conclusion is that schizophrenia is basically organic. Perhaps it is, but to me schizophrenia is such an enormous process, such a complicated disease of so many varieties, that it is too early to come to any definite conclusion about it. It is my opinion that all is not yet known about schizophrenia; it will take a long time before one will be able to tell definitely what the underlying process is. Meanwhile, I think Dr. Schilder's conclusions are correct, in the light of his observations.

Dr. Nolan D. C. Lewis: The subject of schizophrenia is so extensive that one is apt to become confused in attempting any comprehensive discussion. If the subject were not so large—as large, in fact, as the general subject of cancer—one would say that the problem has already been fairly well covered this evening. There are so many aspects of this disorder, however, as indicated by Dr. Brill's last few words, that one could go on discussing all night the various phases and types of organized and unorganized behavior seen in patients with schizophrenia. However, Dr. Schilder's paper has raised some important points for consideration, and my few remarks will be limited to these. When he said that schizophrenia has an organic nucleus and, at the same time, emphasized the reaction in terms

of psychogenesis, I thought that his attitude would seem paradoxic to many in the audience. I shall not attempt to explain Dr. Schilder's meaning in any detail, as he is present to speak for himself. However, my own interpretation of his attitude is that he does not mean to translate observations or facts from one category to another. In other words, he is not thinking in terms of which is first, the hen or the egg, but he is considering the total organization of the individual patient. There are the various structures and the functions which serve the aims and ends of the total personality or of the person. The various drives and needs naturally utilize the structures and materials available; in other words, they utilize the relation which has become established during the evolutionary process. There are the organic structural nuclei which, in my opinion, are predisposed or organized in the constitution during its development, so that under certain conditions and in certain persons they produce specific reactions.

The laws of integration are such that one could probably reconstruct the whole person from any starting point, either in the structural or in the functional organization. I find no difficulty in speaking of the different aspects of the person or of the situation. There is another point I wish to mention. If I understood Dr. Schilder correctly, it is his theory that the schizophrenic person is threatened in early childhood and withdraws into a position that is more secure, in an attempt, by the utilization of various mechanisms, to increase the importance of his own personality. In other words, the schizophrenic person retreats into a psychosis in which the primitive threat is renewed by the dangerous situation occurring in everyday life. I consider this an important interpretation.

A number of years ago, in a study which I made of patients with prolonged schizophrenia, I saw many illustrations of this concept. The patients in this group had gone through the acute phases of schizophrenia and had settled down to become permanent institutional charges. They had made a readjustment on the simple level of protected hospital life. In a number of cases, the various delusions, hallucinations and other symptoms for which they were admitted to the hospital dropped into the background, and the patients carried on their lives at what might be interpreted as a higher level. They could converse in an intelligent way on matters of the day, politics and other subjects; they could easily be presented to an audience as normal persons. However, if at any time the examiner became actively critical or crowded the patient with annoying questions, the whole attitude of the patient changed to a point at which expressions of the psychosis came into the foreground. In such situations, some of the patients spoke in a delusional way, making such statements as: "I grew from a seed"; "I am ten thousand years old"; "I am the oldest man in the world." In other words, the statements were in outstanding contrast to the former conversation. In this behavior one has a retreat into the delusional system. Dr. Schilder also emphasized that the disturbances in the perceptive and in the motor faculties are not the same as those observed in patients with gross lesions of the brain. I wonder if he has studied the patients who show combinations of reactions? For instance, many patients with organic disease of the brain, in addition to the reactions long known as "organic mental reactions," exhibit a behavior which resembles the schizophrenic type, or at least has all the clinical aspects of schizophrenia. It is sometimes sharply in the foreground in patients with dementia paralytica. I have seen many patients with dementia paralytica, as well as with other organic diseases of the brain, whose condition would certainly have been diagnosed as schizophrenia if laboratory and neurologic findings had not been available. In some cases dementia paralytica is notoriously hard to differentiate from catatonic dementia praecox before the laboratory findings are available. I wonder what the experimental investigations, such as those carried out by Dr. Schilder, would show in combinations of this sort? Is there anything in the field of psychologic experimentation that indicates a difference?

Another point that I wish to mention briefly concerns the attitude of patients who have recovered toward their disorders. When the patient has a spontaneous

recovery or recovers under the ordinary hospital regimen, without any special therapy, he usually discusses his previous symptoms very little. He is shy and embarrassed and sometimes seems afraid or reluctant to describe previous symptoms in any detail. Often, a patient will say that he wishes to forget the whole matter and put it in the past. Such a patient is often discharged as socially recovered, but he is obviously trying to suppress his insight. He may have insight, but he cannot or does not express it easily. This reaction is in contrast with that of patients recovering under active organized psychotherapy. A recovery in this situation is usually accompanied by degrees of deep understanding of the various problems. The patients speak freely about their previous symptoms and will cooperate in any attempt to make a final evaluation of the degree of restitution and the possibilities for the future.

The patient who recovers after insulin therapy usually emerges from shock without deep insight. He has what I call descriptive insight. He will talk freely about his delusions, hallucinations and other symptoms, but not in the same way as the patient who has had a long course of psychotherapy. The insight is more superficial, on the one hand, than that of the patient who has had psychotherapy, while, on the other, it is more freely expressed than that of the patient who recovers spontaneously.

DR. PAUL SCHILDER: I confess that I felt courageous when I endeavored to discuss the psychologic aspects of schizophrenia in thirty-five minutes; I knew from the beginning that such an endeavor would be incomplete. I restricted myself as much as possible to psychologic problems, and therefore did not mention the confirmatory evidence which Dr. Hinsie has brought forward. I wish to make only one remark about the psychophysiologic relations. I ask you to think of a person who has been intoxicated with mescal. I have analyzed such persons. An organic agent is involved; yet the intoxication is full of meaning from the patient's point of view and cannot be understood unless one knows his individual life. I mention mescal intoxication especially because many of its phenomena, especially the parieto-occipital disturbances, show great similarity to those of schizophrenia. I may here refer to the remark by Dr. Lewis, which is indeed valuable, that one finds in cases of dementia paralytica pictures which are difficult to differentiate from schizophrenia. I wish to point out a group of cases of dementia paralytica described by Gerstmann in which, when the malaria treatment was over, a schizophrenic picture developed which could not be differentiated from schizophrenia. It developed, however, in another order of events. Really, therefore, the problem of psychophysiologic relations is not as complicated as many would like to think. It is comparatively simple if one sees the facts as clearly as possible and draws conclusions, facing the danger of making mistakes.

FEAR AS A THERAPEUTIC AGENT. DR. OSKAR DIETHELM.

The institutional and noninstitutional use of fear as a therapeutic agent and its occurrence in hospitals and private practice are discussed. The relationship of the patient and the physician is studied from this point of view. The physician's philosophy will influence his therapeutic use of fear. The more he believes in education of patients rather than reeducation of unhealthy psychobiologic habits based on an analysis of the personality the more he will feel justified in resorting to discipline, punishment and reward, fear and hope. Fear is, therefore, used primarily in the correction of behavioristic difficulties in children and of psychotic misbehavior. It is further used in reeducation of psychopathic personalities and of highly involved neurotic reactions. It may be that the purposeful use of fear is not recommended any longer. Unintentional use of fear therapy and fear occurring in physiologically planned treatment, however, are important even now, and will be in the future. Only by recognition of this fact will the control and increasing elimination of fear as a therapeutic agent become possible.

DISCUSSION

DR. EDWIN G. ZABRISKIE: Although I have read Dr. Diethelm's paper with interest, it seems to me that there are one or two factors which should be considered carefully before the employment of any such therapeutic measure as fear is undertaken. It is important to distinguish the various types of fear which, I think, exist. For instance, the fear that governs the hypochondriac person is not the same factor as the fear of losing his job that impels a man with some type of injury to get well. I think there is a difference in the two reactions. It is largely governed by the individual person and the way he reacts to the fear stimulus, if I may use that term, but it is still a factor that should be evaluated, if one attempts to employ such an agent therapeutically. In my practice, I attempt to overcome the various fear reactions that I encounter in patients and try to give them what seems to me a rational explanation of their fears.

As regards the fear reaction in psychotic patients, particularly those in hypoglycemic and metrazol shock: While all are inclined to accept the explanation of its role in recovery, at least in some cases, the parallel series reported from the Westchester division of the New York Hospital is instructive. There was little difference between the results in a series in which insulin shock was used and those in one in which extra care was used.

Therefore I do not see how fear of unpleasant experiences is of great importance.

A patient gave me a graphic description of how fear drove her to analysis, how fear kept her on tenterhooks during the analysis and how fear of being thrown out into the world and of losing contact with the analyst prolonged her neurosis, or so she thought. I ask Dr. Diethelm to explain, if he can, whether he considers that there are various types of fear.

DR. CLARENCE P. OBERNDORF: In my experience, fear is rarely a prominent therapeutic agent in the treatment of neuroses or psychoses. I can conceive of fear acting as an incentive to impel a man to seek treatment and thereby, indirectly through fear, to receive the benefits of psychotherapy. Fear as a psychotherapeutic agent is old in its application. The older textbooks contain many reports of cases in which fear temporarily altered the course of a psychosis or neurosis. Recently, I secured a book entitled "Tentamen therapeuticum de animi perturbationibus." It was written in 1783 by a student in medicine at Montpellier, France, as a thesis for graduation. He discussed in detail the application of fear through such contrivances as ducking and the rotating chair, which Dr. Diethelm has mentioned, and showed how certain reactions to these punishments and certain threats had changed the course of a mental disorder. In a footnote, he cited Boerhaave, the well known Dutch clinician, a man whom Henry Sequist compared with Osler and whose fame rests on his extraordinary acumen as a clinician. In an orphan asylum outside Haarlem, Netherlands, early in the seventeenth century, there occurred an epidemic of convulsions. Nothing could alter the infectious nature of this epidemic. So Boerhaave was called. He had an iron rod heated to glowing heat and threatened to burn to the bone the next child who had a convulsion. According to the reporter (and the account is long), the therapy was successful in the majority of cases, but one child was so frightened that he died "on the spot."

This episode may be used as a transition to the present day concept of the use of psychotherapy. When I first entered this field, about 1908, there was in use the modern counterpart of the red hot iron—the Paquelin cautery. To prepare myself for the practice of psychiatry, I acquired an ophthalmoscope, a percussion hammer and a Paquelin cautery. I never used the last, because about that time the concepts of Freud, emphasizing the necessity of finding the underlying causes of fear—especially unconscious ones—began to permeate psychiatric thought. I come, therefore, to the comment of Dr. Zabriskie that there are different kinds of fear. I do not think it is permissible to ignore the value of anxiety as a protective agent in the neuroses.

I do not wish to discuss freudian ideas in too great detail, but I think there is a difference between fear and anxiety. Freud first observed that anxiety was merely a form of free floating, unmobilized sexual libido. Later, he changed his concept of anxiety and expressed the belief that it is mobilization of the life force as a defense in the face of a threat coming from external or internal sources. Freud recently said that one is not now so much concerned with the nature of anxiety. I think that it is important, however, to learn of what anxiety and fear are composed, especially in the light of the biochemical discoveries of the past few years.

This brings me to the latter part of Dr. Diethelm's paper, in which he mentions metrazol. Are shock and fear the same? Does shock produce the same change in the body as is instigated by fear? Does insulin shock act in the same way as the fear which brought about the change in patients in 1783—a change in the thought and the energy reaction? It is an interesting question to ponder. It seems that the physiologic shock and the fear reaction may bring about an analogous interruption, perhaps in the habitual organic structural currents which have been established by thought habits of these persons. Such interruptions may produce a change which permits reorganization and readjustment of the thought flow, thereby acting as a therapeutic agent. I am grateful to Dr. Diethlem for bringing up this topic. It is an unsolved question; only too often, as he pointed out, the various disciplinary measures used in the hospitals may be interpreted by the patients as agents of fear.

DR. OSKAR DIETHELM: Dr. Oberndorf has answered to my satisfaction Dr. Zabriskie's question about the different types of fears. I agree with what he said. The other remarks were amplifications of parts of the paper which I did not discuss sufficiently.